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HANDBOOK OF NUTRITION

A SYMPOSIUM

Prepared Under the Auspices of the Council
on Foods and Nutrition of the
American Medical Association

1943

AMERICAN MEDICAL ASSOCIATION

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CHAPTER I

INTRODUCTION

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BIRMINGHAM, ALA.

The most fertile field in the world of medical research today is nutrition. The yield is good and even in time of war the product compares favorably in value with that of the industries. To weigh these values critically, to correlate them, to examine them in their relation to medical practice and human welfare, and then in the light of the information thus gained to revise present day knowledge is the object of this series of special articles on nutrition.

The advances which have been made in the science of nutrition within the past few years fire the imagination. Vitamins have been produced in pure form and their functions defined with a fair degree of clearness, and as a result a more intimate knowledge has been gained of the intricacies of metabolism; the essential nature of fats has been demonstrated; the roles of proteins and minerals in human economy have been further elucidated; the amounts in which all these necessary substances are required by man have been expressed in figures, and the foods which provide them most abundantly have been determined. Finally, there has developed a clearer understanding of the deficiency states with a fuller appreciation of the frequency with which these states impair man's usefulness and destroy his happiness. This marks an era of signal achievement.

Such discoveries, however, seldom tell the whole story. They clarify problems and give useful information, but not infrequently their most significant result is to increase the scope of the student's vision and to open up new vistas for further exploration. Constantly, new problems present themselves. Consider, for example, the relationship of vitamins to enzymes. Some are co-enzymes and are known to unfold their specific activities while serving as the prosthetic group of the enzyme molecule. Is all vitamin activity of this nature? Witness too the need for more complete data concerning man's requirement for the vitamins of the B com-

plex, notably riboflavin and nicotinic acid, and also for further information concerning the full function of ascorbic acid, one of the most thoroughly studied of the vitamins. How pressing is the need of the adult for vitamin D? Do the requirements for all vitamins, as is true of some, vary with circumstances? And what are the circumstances? To what extent does each of the known vitamins influence the requirement for the others? Is there such a thing as an optimum ratio between vitamins, and what is the result when this ratio is grossly upset? Will the administration of one vitamin precipitate symptoms due to the latent deficiency of another? In truth, the story of the vitamins is just beginning.

The same is true of the mineral elements. It would be of advantage to know, for example, more about the influence of the various life periods on human requirements for calcium and phosphorus and about the influence of the other inorganic elements on the availability of copper and iron. Of clinical interest too are the hazards to which the latter element is subjected in its absorption from the intestinal tract. One of the newest problems deals with the role played by the so-called trace elements in animal metabolism. There are indications that it is not an unimportant role.

Then come even more practical questions. After ages of experience in gathering, storing and cooking food, man is now beginning to inquire concerning the effect of all this on nutritive values. Only today he has learned that vegetables improperly gathered and permitted to remain hours upon hours on display at the grocer's lose much of their nutritive value and that the bottle of milk left on his doorstep in the bright sunlight will within the hour be deprived of a large part of its riboflavin. Even the effect of cooking on the digestibility and availability of the various proteins is not fully understood. Insistent questions too are being asked by nutritionists as to the effect on foods of storing, drying, freezing, sterilizing, pasteurizing and milling. Indeed, the influence of all forms of processing is under investigation.

Technical procedures suitable for clinical use are needed. The recognition of nutritive deficiency is often difficult because of the paucity of precise methods by which a person's nutritive status in respect to each of

the known vitamins can be measured. The dark adaptation test for vitamin A deficiency and the slit lamp method for revealing the small vessels in the cornea, which tell of riboflavin deficiency, are of promise, but the pressing need is for special technics by which biochemical changes can be measured. By such methods it is possible today to recognize in the blood a deficit in proteins, ascorbic acid or vitamin K, but the other technics which have been developed are not available for clinical use. Then too there are more fundamental difficulties. One of these lies in the fact that figures obtained from the blood do not necessarily tell of the adequacy with which the body is equipped with a given substance. The amount of a vitamin held in the blood may not begin to fall until the stores of that substance in the tissues are almost exhausted, and it is the state of the tissues that really tells the story. In addition, there is a need for more dependable standards. It is a mistake to assume that the so-called normal subject, chosen because of his healthy appearance, is necessarily normal in respect to his vitamin equipment. Standards should be obtained, not from the general population, but preferably from groups of persons whose intakes of all nutrients for a definite period are known to have approached the optimum, and, when feasible, these standards should also refer to age and occupation groups. Until the special technics are of wider availability and standards are more dependable the physician must continue to depend largely on his clinical acumen.

Research in nutrition has not been limited to the study of single essentials. Food products are being investigated in the effort to point out those articles which are especially rich in essential substances and those which have good supplementary values. The effort is being made also to improve the quality of cheap staple foods, as is seen in the development of enriched flour, in the fortification of oleomargarine with fish liver oils and in the addition of iodine to table salt. Such restoration of important substances lost in processing, as in the case of enriched flour, is being encouraged, but it should be noted that, with two exceptions (the addition of vitamin D to milk and vitamin A to butter substitutes), the Council on Foods and Nutrition of the American Medical Association does not approve of the addition to foods of substances not found in the native

article or in amounts in excess of the amount carried by the best foods of its class. The attempt to convert a food into a pharmaceutical product is frowned on, but the restoration of substances lost in preparing the food for the market is a recognized part of the nutrition program.

The government also is interested in nutrition, vitally so in these perilous times of war. To wage successful war a nation must possess not only armed forces of surpassing valor, well equipped, but also, supporting these, a people of inflexible stamina. This last demands that the population be well fed. If their food is lacking in kind or amount they will be wanting in industrial efficiency and nervously unstable. To produce the food required, to get it to the people and then to induce them to use proper selection in its eating are problems of agriculture, transportation, commerce and education, all of which in turn are problems of government. The state is becoming acutely aware of its obligations in this regard, as was evidenced in the calling by the President of the nutritional conference for defense, in the formation of the Food and Nutrition Board of the National Research Council, in the activities in this field of the Federal Security Agency, and in the increased interest shown by the Food and Drug Administration in accuracy in labeling and truthfulness in advertising. Through these agencies, measures are being developed for the protection and education of the consumer, and increasing governmental regulation of the production, processing, storage and sale of food may be expected. If this is wisely done, benefits will accrue.

But, it is asked, is all of this in truth as important as would appear? Is the average American diet susceptible of great improvement? I would unhesitatingly answer yes. If some physicians answer no, it is perhaps because they are not looking at the whole picture. True, outspoken deficiency diseases are relatively rare in American hospitals—at least they seldom stare one in the face—but this is not the type of deficiency of which I write. The type which in point of numbers bulks largest is the milder type, often expressed by borderline states of nutritive failure in which the person is neither grievously sick nor entirely well. Scrutiny of the life histories of patients and studies of their personality have shown that the earliest effects of nutritive deficiency are

not to be found in the polyneuritis of beriberi or in the bleeding gums of scurvy or in the dermatitis of pellagra but rather in the mental depression, nervous instability and other forms of vague ill health which almost always come first. Indeed, the severer, more outspoken manifestations may remain indefinitely in abeyance; the patient is simply called a neurasthenic, or such terms as inadequate personality and constitutional inferiority are applied. After watching these patients, one is impressed by the truth of the statement that no greater catastrophe comes to man than the loss of efficiency, the lack of initiative and the mental depression which accompany nutritive failure. Evidence that these more elusive forms of nutritive deficiency are not rare but in reality are of frequent occurrence can be found in the other articles of this series and in the recent report of Jolliffe, McLester and Sherman.¹

The prevention of the disorders just enumerated, however, is not the only object of present day studies in nutrition. A far wider objective is sought—the improvement of the race. This is not beyond reason; take two examples. Consider first the success of feeding experiments with the lower animals. Students of nutrition have been able through intelligent additions to a ration which already was regarded as adequate so to improve the albino rat in respect to stature, vigor, fertility and longevity as to produce in the course of years a superior race of animals. Then compare the children born in this country of immigrant parents with their forebears and note their superiority in physical and mental characteristics. Though not so striking, a similar trend can be seen in children born of American stock. This superiority can be attributed to the better environment enjoyed by these children, an important feature of which has been a more adequate diet. To students of nutrition this points the way to the development of a larger, more vigorous race.

Ever since man's early ancestors first climbed out of the sea and began to forage on land, he has been able through gradually increasing control of his environment steadily to improve the nature of his food. This has been a potent factor in the evolutionary process that has made him dominant as a species and has kept him so for

1. Jolliffe, Norman; McLester, J. S., and Sherman, H. C.: The Prevalence of Malnutrition, *J. A. M. A.* 118: 944 (March 21) 1942.

thousands on thousands of years. Biologic history, however, contains numerous examples of evolution of a species which was followed in time by involution. The effort today to adjust human environment to physiologic needs is expected to prevent the latter process, but as to its ultimate success genuine doubt may be entertained.

The trend of improvement in man's nutrition continues. In attractiveness, keeping qualities, palatability and digestibility his food today is superior to that of his immediate forebears, but it has also suffered losses. Because of the refinements to which it has been subjected it often fails to carry vitamins, minerals and other essential substances in the abundance supplied by the earlier foods. Is it possible that these disadvantages will in time outweigh the advantages and lead finally to a halt, even to a retrogression, in the development of the race? And can this be prevented through the application of the recently gained knowledge of nutrition? Or, still better, is it possible by means of this knowledge to carry forward, even accelerate, man's upward progress? The answer can be sought in the special articles which follow.

CHAPTER II

PROTEINS IN NUTRITION

HOWARD B. LEWIS, PH.D.

ANN ARBOR, MICH.

The term protein was suggested by the Dutch chemist Mulder in 1839 as a designation for the universal component of tissues, both plant and animal. Protein was characterized by him as "unquestionably the most important of all known substances in the organic kingdom. Without it no life appears possible on our planet. Through its means the chief phenomena of life are produced."¹ Some sixty years later the primary importance of the proteins was again emphasized by Verworn,² who wrote: "The proteins stand at the centre of all organic life." Today, more than a century after Mulder, the proteins are still "first" (Greek, *πρωτεῖος*) in the regulation of vital processes, and disturbances in their metabolism are associated with nutritive failure and with many pathologic conditions with which the physician is confronted.

Proteins are normal constituents of all animal cells and body fluids with the exception of the bile and the urine. They are essential components of both the protoplasm and the nucleus of the cell; hence they exert a profound influence on growth. They are important in the regulation of osmotic relations between cells and intercellular fluids and between tissues and blood and play a significant role in the fluid balance of the body. Many of the best characterized enzymes have been obtained in crystalline form and have the properties of proteins (the "protein enzymes").³ A considerable number of the hormones, chemical regulators of the body, are either proteins (the so-called protein hormones)⁴ or are derivatives of proteins. Many of the substances associated with immunologic and antigenic

1. Mulder, G. J.: *The Chemistry of Animal and Vegetable Physiology*, quoted by Mendel, L. B.: *Nutrition: The Chemistry of Life*, New Haven, Conn., Yale University Press, 1923, p. 16.

2. Verworn, M.: *General Physiology*, London, Macmillan Company, 1899, p. 479.

3. Northrop, J. H.: *Crystalline Enzymes*, New York, Columbia University Press, 1939.

4. White, A.: *Protein Hormones*, in the *Cold Spring Harbor Symposium on Quantitative Biology*, Cold Spring Harbor, L. I., N. Y., The Biological Laboratory, 1938, vol. 6, p. 262.

reactions and similar phenomena are known to be proteins. Finally, in recent years the causative agents of certain virus diseases (notably the tobacco mosaic and the bushy stunt of the tomato) have been obtained in crystalline form and exhibit the characteristic properties of proteins, yet when inoculated into the proper host they multiply and give rise to the specific pathologic changes associated with the virus.⁵ The study of "virus proteins" has become of increasing importance.

It is notable that the proteins exist as large molecules or possibly aggregates of molecules. In table 1 are presented the probable molecular weights of a few important proteins, as summarized by Svedberg and Pedersen.⁶ The large molecules of even the simpler proteins may be compared with those of some other important constituents of tissues or body fluids: sodium chloride, 58; urea, 60; ascorbic acid, 176; dextrose, 180; lactose, 342; carotene (provitamin A), 537, and glyceryl tristearate (a typical fat), 891.

When this large protein molecule is broken down by the addition of the elements of water (hydrolysis), a considerable number of much simpler units or building stones are formed whose molecular weights range from 75 (aminoacetic acid, known also as glycocoll or glycine) to 240 (cystine). These units have the structure and properties of anpholytes (dissociation so that they may function either as an acid or as a base depending on the p_H of the environment) and are known as α -amino acids. From the chemical standpoint, they are characterized by the presence of a carboxyl (COOH) group with acidic properties and an amino (NH₂) group with basic properties, the two groups being attached to the same carbon atom.

The character of the remainder of the amino acid molecule (designated by R, fig. 1) varies, but all the typical products of hydrolysis have in common the presence of the carboxyl and amino groups. Important chemical grouping in various amino acids are sulfur (cystine and methionine), hydroxyl (threonine and serine), benzene nucleus (phenylalanine and tyrosine), guanidine nucleus (arginine), indolyl ring (tryptophan) and imidazolyl ring (histidine).

5. Stanley, W. M.: *Some Chemical, Medical and Philosophical Aspects of Viruses*, *Science*, **63**: 143-151 (Feb. 14) 1941.

6. Svedberg, T., and Pedersen, K. O.: *The Ultracentrifuge*, Oxford, England, Clarendon Press, 1948, p. 406.

Certain units or amino acids present in the protein molecule are considered of especial importance in the structure of tissue (growth) and are commonly designated as the essential amino acids. The chemical nature of these essential units will be discussed subsequently. The formulas of the other amino acids may be obtained from any of the numerous standard textbooks on biologic chemistry.

The amino acids are joined to each other in the protein molecule by a linkage known as the peptide linkage, in which the basic (amino) group of one acid is linked to the acidic (carboxyl) group of the adjacent acid with the loss of a molecule of water. A compound made

TABLE 1.—*Sources and Probable Molecular Weights of Proteins*

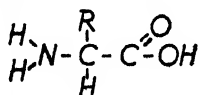
Protein	Source	Probable Molecular Weight
Lactalbumin.....	Milk	17,000
Lactoglobulin.....	Milk	35,200
Zeln.....	Corn	35,200
Pepsin.....	Gastric juice	35,200
Insulin.....	Pancreas	35,200
Bence Jones protein.....	Urine	35,200
Ovalbumin.....	Egg white	35,200
Hemoglobin (man)....	Erythrocytes	70,400
Serum albumin (horse).....	Blood	70,400
Serum globulin (horse, man)....	Blood	140,800
Edestin.....	Hemp seed	282,000
Urease.....	Jack bean	422,000
Thyroglobulin.....	Thyroid	650,000
Antipneumococcus serum globulin....	Horse blood	845,000
Bushy stunt virus.....	Tomato plant	7,600,000

up of two acids thus joined is known as a dipeptide, and a similar compound which contains several (usually an unknown number) amino acids bound together in the peptide linkage is known as a polypeptide.

Hydrolysis of the dipeptide for which the formula is given would break the peptide linkage (—NH—CO—), and the component amino acids would be obtained. While the peptide linkage may not be the only linkage between the amino acids of the protein molecule, it is certainly by far the most important one. This is borne out by the chemical properties of native proteins (proteins as they are found in nature as contrasted with derivatives formed by the action of heat, alcohol, water, salts, enzymes and the like). The biologic reactions of the proteins are also more closely related to those of amino acids than to those of any other type of hydrolytic product of protein, such as proteoses or peptones.

Just like the amino acids, which are ampholytes and may react with either acids or bases, depending on the p_H of their environment, the proteins as complexes of amino acids (polypeptides) may combine with either acids or bases. For the most part, the proteins as they exist in fluids and tissues of the animal organism function as acids (play the role of anions) and are in combination with bases (cations). Thus the protein hemoglobin of the erythrocytes is combined in the cell with bases (chiefly potassium) as a salt; similarly milk contains various salts of casein, of which calcium caseinate is important.

When two amino acids are joined in peptide linkage, two different peptides may be obtained; with three amino acids, six peptides, and with five amino acids, 120 peptides. These are known as isomers, since they are all made up of the same units and have the same percentage composition. They differ, however, in the



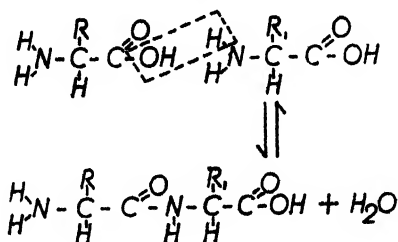
An alpha amino acid

arrangement of the amino acids in the peptide chain (for instance, in the case of a tripeptide, a-b-c, a-c-b, b-a-c, b-c-a, c-a-b and c-b-a, when a, b and c are three different amino acids). Since more than twenty amino acids are known to be of general occurrence in the protein molecule, it is obvious that the possible number of isomeric proteins (polypeptides) is very large. A peptide made up of the twenty amino acids most commonly obtained in the hydrolysis of protein, each acid occurring once only in the chain, would have a molecular weight of 2,499. A simple calculation shows that the number of possible isomers of this peptide would be 2,432,902,008,176,640,000, a number beyond the range of human thought.⁷ Each of these peptides would have the same percentage composition, would yield the same amino acids on hydrolysis in the same proportions and would have similar properties. Each would differ from the other in some slight variation in the arrange-

⁷ Abderhalden, E.: *Lehrbuch der physiologischen Chemie*, ed. 6, Berlin and Vienna, Urban und Schwarzenberg, 1931, p. 302.

ment of the component amino acids of the peptide chain. Each would therefore be a chemical individual distinct from the other isomeric peptides.

If it is remembered that the protein molecule is much larger than that of the peptide just discussed, that native proteins vary greatly in the amounts of amino acids which they yield on hydrolysis and that some linkages other than the simple peptide linkage almost certainly occur in the protein molecule, it is evident that the possible number of different proteins as they exist in nature is almost infinite. This individuality of natural proteins finds expression in the so-called specificity of the proteins. This may be most simply defined by the statement that every species tends to construct within the organism a protein characteristic of that species.



Formation of a dipeptide

Thus, casein of cow's milk is believed to differ from casein of goat's milk, protein of beef muscle to differ from protein of pork muscle and serum protein of human blood to be different from serum protein of beef blood. While in my opinion the basis of this specificity is undoubtedly chemical and is related to the possibilities of isomerism just discussed, this cannot be proved at present. The specificity of proteins of different biologic origin must for the present be demonstrated by biologic reactions, by the reactions observed when "foreign" protein is introduced into the organism. The phenomena of anaphylaxis, of antibody formation, of food allergies and of many other antigenic and immunologic reactions are all manifestations of this biologic specificity of the proteins, so important in many considerations of medical practice.

The protein of the human diet is obtained from both animal and vegetable sources. Among foodstuffs of

animal origin, meats (both muscular and glandular tissues), fish, eggs, milk and milk products are most important. Vegetable protein is most readily available in the cereal grains (wheat, corn, rice, rye and barley), the seeds of legumes (peas and various kinds of beans) and many nuts, of which the peanut is perhaps most important in the human diet. It is estimated that the cereals contribute about 25 per cent of the total calories of the diet of the American people.

The proteins of the foodstuffs, large molecules with colloidal properties, do not diffuse readily through biologic membranes. If these dietary proteins are to be utilized, it is necessary that they be altered so that passage through the mucous membrane of the intestine is possible. This is accomplished in the gastrointestinal canal by the process of digestion, by the action of a group of biologic catalysts or enzymes, whose activities are so coordinated as to effect a rapid and complete hydrolysis to the soluble diffusible amino acids. Since biologically the amino acids are nonspecific, digestion results in the loss of the biologic specificity of the proteins; if this were not the case, large amounts of "foreign" protein would normally enter the blood stream from the alimentary canal, and food allergies of protein origin would be of very frequent occurrence. In the words of the English physiologist Cathcart:⁸ "It is the disintegration of the specific protein to its constituents which are for the most part non-specific which would seem to be the characteristic function of digestion; the breakdown of the colloidal non-dialyzable whole protein to the dialyzable simple peptides and amino acids."

The enzymes concerned in this process are pepsin and rennin of the gastric juice, trypsin and chymotrypsin of the pancreatic juice and a group of enzymes known as peptidases, which are present in the pancreatic and intestinal juices and hydrolyze the peptides. (It should be noted that commercial "trypsin" and the trypsin referred to in the older literature are mixtures of the proteolytic enzymes of pancreatic tissue and include not only trypsin but also chymotrypsin and peptidases.⁹) Digestion is best effected if these enzymes act on the

8. Cathcart, E. F.: *The Physiology of Protein Metabolism*, in *Monographs on Biochemistry*, ed. 2, London, Longmans, Green & Co., 1921, p. 3.

9. Northrop,⁸ pp. 62-63.

proteins of the diet in the natural anatomic sequence, i. e., gastric, pancreatic and intestinal.

Digestion proceeds rapidly in the intestine; the amino acids are absorbed as rapidly as they are formed by the activity of the enzymes. Although digestion studies in vivo with experimental animals with fistulas at various levels throughout the alimentary canal have clearly demonstrated that the major portion of the ingested protein is completely hydrolyzed to amino acids, or at least to very simple peptides,¹⁰ the question of the absorption of some portion of the protein of the diet in unaltered form into the circulation must be considered. Early workers whose experimental methods were not adequate were led to favor the possibility of such an absorption under unusual circumstances, particularly in young animals, in which the intestinal membrane was assumed to be more readily permeable. The use of the newer methods of immunology, by which accurate detection and differentiation of very small amounts of specific proteins have been made possible, has thrown new light on the question. By these methods it now appears to have been demonstrated that in many persons, without regard to age or sex, a detectable amount of certain proteins frequently enters the blood stream in an unaltered state via the alimentary canal. As Walzer¹¹ has expressed it, "The regularity with which the phenomenon occurs in the average individual and the uniformity of results when repeatedly tried under identical conditions on the same subject, preclude the possibility that this is an accidental or unusual occurrence." Of the protein foods studied, the most extensive observations have been reported with egg white.¹² These findings are of special significance in relation to the phenomena of sensitization to specific protein foods. However, it should be remembered that

10. Abderhalden, E.; Kautzsch, K., and London, E. S.: Studien über die normale Verdauung der Eiweisskörper im Magendarmkanal des Hundes, *Ztschr. f. physiol. Chem.* **48**: 549-556, 1906. Abderhalden, E.; Baumann, L., and London, E. S., *ibid.* **51**: 384-390, 1907.

11. Walzer, Matthew: Studies in Absorption of Undigested Proteins in Human Beings: I. A Simple Direct Method of Studying the Absorption of Undigested Protein, *J. Immunol.* **14**: 143-174 (Sept.) 1927.

12. Wilson, S. J., and Walzer, Matthew: Absorption of Undigested Proteins in Human Beings: IV. Absorption of Unaltered Egg Proteins in Infants and Children, *Am. J. Dis. Child.* **50**: 49-54 (July) 1935. Ratner, Bret, and Gruehl, H. L.: Passage of Native Proteins Through the Normal Gastrointestinal Wall, *J. Clin. Investigation* **13**: 517-532 (July) 1934. The observations with egg white are of interest in view of the studies which show poor utilization of the proteins of raw egg white. Compare Bateman, W. G.: The Use of Raw Eggs in Practical Dietetics, *Am. J. M. Sc.* **153**: 841-855 (June) 1917.

the methods of immunology are capable of detecting exceedingly minute amounts of protein and that the total amount of protein absorbed thus unaltered must be very slight. One may, then, with a reasonable degree of confidence look to the behavior of the individual amino acids for the interpretation of the role of protein in normal nutrition.

The products of the digestion of proteins, chiefly the amino acids, enter the portal blood on absorption from the intestine and are distributed to the tissues by the systemic blood. The postabsorptive increase in the amino acid nitrogen of the blood, although not large, is unquestioned. The amino acids are rapidly taken up by the tissues, and the amino acid content of the blood returns to normal.¹³

One of three fates awaits the amino acids which thus enter the cell. The first is condensation with other amino acids, selected by the particular tissue in question from the pabulum supplied to it by the blood, to form the protein characteristic of that particular tissue or cell. This specific synthesis, the converse of digestion, makes possible the maintenance of the individuality of the cell. This process acquires a particular significance in young animals in which building of new tissues, growth, must occur for normal development and in the adult in normal pregnancy and lactation.

A second metabolic path is utilization of the amino acids for some special purpose in the animal economy apart from the general synthesis of cellular protein. Examples of this are the synthesis of such proteins as hemoglobin, fibrinogen and the serum proteins. Amino acids are utilized also for the formation of specific proteins with hormonal function (insulin and prolactin) or amino acid derivatives which are hormones (epinephrine and thyroxine) or chemical regulators which are not usually classed as hormones (glutathione, histamine and creatine). The synthesis of the "protein enzymes" (pepsin, trypsin, catalase and carbonic anhydrase) also occurs. The details of the reactions which lead to the synthesis of such specialized proteins and protein derivatives are not as yet clearly understood.

After the needs of the cells for these two purposes have been met, an excess of amino acids may still remain

13. Van Slyke, D. D.: The Present Significance of the Amino Acids in Physiology and Pathology, *Arch. Int. Med.* 19: 56-78 (Jan.) 1917; *Physiology of the Amino Acids*, Science 95: 239-263 (March 13) 1942.

in the cells. The fate of this amino acid fraction is deamination—removal of the nitrogenous portion of the molecule—and utilization of the non-nitrogenous portion, since in contrast to fat and carbohydrate storage of protein or amino acids for any considerable time does not appear to be possible. The nitrogenous fraction of the molecule, split off as ammonia, is rapidly converted into urea under normal conditions and is eliminated in this form by the kidneys. The efficiency of this transformation is demonstrated by the fact that normally systemic blood contains less than 0.1 mg. of ammonia nitrogen per hundred cubic centimeters, while the urea content of normal blood calculated as urea nitrogen is approximately 17 mg. per hundred cubic centimeters. The non-nitrogenous residue which remains after deamination may either be transformed into dextrose and used in this form, the antiketogenic fraction of the protein molecule, or be converted to fatty acids, the ketogenic fraction of the protein molecule. Whether the non-nitrogenous residue is converted to dextrose for utilization in that form depends on the chemical structure of the original amino acid. In general one may say that about half of the amino acids present in the molecule of any individual protein may give rise to dextrose in intermediary metabolism.

Physiologic and nutritional studies alike have emphasized the role of the amino acids as structural elements, the building stones of living protoplasm. What are the amino acid requirements for the construction of new cells? Are all the amino acids of equal importance in nutrition? These questions have been answered in part by the studies of Rose, which were based on the pioneer work of Hopkins and of Osborne and Mendel. It should be emphasized that the discussion immediately following concerns the requirements for growth of one species, the white rat. Rose¹⁴ first demonstrated that it was possible to obtain normal growth of young white rats when the protein element of the diet was supplied by a mixture of chemically pure amino acids, which included those acids known to be of general occurrence in the protein molecule. The effect of the removal of the various individual amino acids from this

14. Rose, W. C.: *The Significance of the Amino Acids in Nutrition*, Harvey Lectures, Baltimore, Williams & Wilkins Company, 1934-1935, series XXX, p. 49; *The Physiology of Amino Acid Metabolism*, Proc. Inst. Med. Chicago 12: 93-110 (April 15) 1938.

mixture was then studied. The absence of certain acids from the diet resulted in impaired growth or in some cases considerable losses in weight and ultimately death. These amino acids, designated as essential, could not be synthesized by the rat and had to be supplied in the diet in adequate amounts or nutritive failure resulted. The withdrawal of other amino acids did not influence the rate of growth. These amino acids, the nonessential amino acids, must therefore be synthesized in the body at a speed commensurate with the needs for normal growth. In tables 2 and 3 are presented Rose's most recent classification¹⁵ of the amino acids on this basis. It has been possible in still further studies to obtain growth in rats fed a mixture of the ten essen-

TABLE 2.—*The Amino Acids Essential for Growth of the White Rat*

Amino Acid	Characteristic Chemical Grouping
Threonine.....	Hydroxy group on 4 carbon chain
Valine.....	5 carbon branched chain
Leucine.....	6 carbon branched chain
Isoleucine.....	6 carbon branched chain
Lysine.....	2 amino groups on 6 carbon chain
Histidine.....	Imidazole nucleus
Tryptophan.....	Indole nucleus
Phenylalanine.....	Benzene nucleus
Methionine.....	Methyl thiol group
Arginine *	Guanido group

* Arginine has a special position, as discussed in the text.

tial amino acids listed in table 2 with the omission of all the acids listed as nonessential. When this essential amino acid mixture was fed at a level of 11.2 per cent of active amino acids normal growth was observed, and at the low level of 5.8 per cent slow growth occurred. In the group of essential amino acids arginine occupies a unique position. Growth is possible in the absence of this amino acid from the diet, but the rate of growth is distinctly less than when arginine is supplied. Rose has defined an indispensable dietary component as "one which cannot be synthesized by the animal organism, out of the materials *ordinarily available* at a speed commensurate with the demands for *normal* growth."¹⁶ If

15. Rose, W. C., and Fierke, S. S.: The Relation of Aspartic Acid and Glucosamine to Growth, *J. Biol. Chem.* **148**: 115-120 (March) 1942.

16. Rose, W. C.: The Nutritive Significance of the Amino Acids, *Physiol. Rev.* **18**: 109-136 (Jan.) 1938. Sentence quoted is on page 129.

this definition is accepted, arginine is classed as essential. This classification of amino acids is one based on the growth requirements of rats. Whether modifications must be made when requirements for pregnancy, lactation or maintenance are under consideration remains to be determined. The possibility of species differences must also be considered. It is known that many of the amino acids are essential for the growth of the young chick. Glycine, however, which can be synthesized by the rat, appears to be an indispensable amino acid for the chick.¹⁷ The limited data available suggest that from the qualitative standpoint the amino acid requirements of the white rat and of man are similar. Holt and his co-workers have studied the effects of the withdrawal of

TABLE 3.—*Amino Acids Not Essential for Growth of the White Rat*

Glycine	Hydroxyglutamic acid
Alanine	Citrulline
Serine	-----
Cystine	Proline *
Aspartic acid	Hydroxyproline *
Tyrosine	Hydroxylysine *
Norleucine	Glutamic acid *

* In his most recent summary, Rose¹⁸ did not include these four amino acids among those whose nonessential character is definitely proved. Earlier work, however, indicated that they were dispensable dietary components.

lysine,¹⁸ tryptophan¹⁹ and arginine²⁰ from the diet of the adult human being. The subjects were fed diets on which maintenance of nitrogenous equilibrium was possible. When either of the first two amino acids was removed from the diet, nitrogen was lost from the

17. Almquist, H. J.: The Amino Acid Requirements and Protein Metabolism of the Avian Organism, Federation Proc., to be published.

18. Albanese, A. A.; Holt, L. E., Jr.; Brumback, J. E., Jr.; Hayes, Marjorie; Kadji, Charlotte, and Wangerin, Dorothy M.: Nitrogen Balance in Experimental Lysine Deficiency in Man, Proc. Soc. Exper. Biol. & Med. **48**: 728-730 (Dec.) 1941. Albanese, A. A.; Holt, L. E., Jr.; Frankston, Jane E.; Kadji, Charlotte N.; Brumback, J. E., Jr., and Wangerin, Dorothy M.: A Biochemical Lesion of Lysine Deficiency in Man, Proc. Soc. Exper. Biol. & Med. **52**: 209-211 (March) 1943.

19. Holt, L. E., Jr.; Albanese, A. A.; Brumback, J. E., Jr.; Kadji, Charlotte, and Wangerin, Dorothy M.: Nitrogen Balance in Experimental Tryptophane Deficiency in Man, Proc. Soc. Exper. Biol. & Med. **48**: 726-728 (Dec.) 1941. Albanese, A. A.; Randall, R. McI., and Holt, L. E., Jr.: The Effect of Tryptophane Deficiency on Reproduction, Science **81**: 312-313 (April 2) 1943.

20. Holt, L. E., Jr.; Albanese, A. A.; Shettles, L. B.; Kadji, Charlotte, and Wangerin, Dorothy M.: Studies of Experimental Amino Acid Deficiency in Man: I. Nitrogen Balance, Federation Proc. **1**: part 2, 116-117 (March 16) 1942.

body, i. e., negative nitrogen balances were obtained. When the missing amino acids were restored to the diet, nitrogenous equilibrium was again obtained. These observations represent, so far as I know, the first convincing demonstrations of the essential nature of specific amino acids in man. Of particular interest was the finding that when arginine was removed from the diet²⁰ the number of spermatozoa in the seminal plasma was greatly reduced. After the restoration of arginine to the diet, the content of spermatozoa returned to normal. Since the testicular tissue of certain fish is known to be exceedingly high in its content of arginine, the authors interpret these findings to indicate that a temporary deficiency of arginine may be met in man by atrophy of the spermatogenic tissue and conclude that arginine also is a human dietary essential. So far as I know, no analyses of the arginine content of human spermatozoa are available. These experiments, which had as one of their objectives "to discover whether deficiencies of particular amino acids produced characteristic pathological changes which could be recognized by clinical or laboratory techniques,"¹⁹ are of great importance, and further details should prove of unusual interest.

In preliminary reports,^{20a} Rose and co-workers have shown that in healthy young men, nitrogen balance could be established and maintained on a level of nitrogen consumption of 7.02 Gm. daily, more than 95 per cent of the nitrogen of the diet being in the form of a mixture of the ten amino acids known to be indispensable for animals. It was thus demonstrated that the twelve amino acids, previously shown to be dispensable for rats and dogs, are also dispensable for man. When valine, methionine, threonine, leucine, isoleucine, or phenylalanine were removed from the mixture of amino acids fed, prompt changes to negative nitrogen balances resulted. Thus the role of these six amino acids as indispensable dietary components for man is established. The removal of histidine from the mixture of amino acids did not influence the nitrogen balance. Hence it is concluded that histidine is probably not necessary for maintenance of nitrogen

20a. Rose, W. C.; Haines, W. J., and Johnson, J. E.: *The Role of the Amino Acids in Human Nutrition*, *J. Biol. Chem.* **148**: 583-684 (Dec.) 1942. Rose, W. C.; Haines, W. J.; Johnson, J. E., and Warner, D. T.: *Further Experiments on the Role of the Amino Acids in Human Nutrition* *J. Biol. Chem.* **148**: 457-458 (May) 1943.

equilibrium in human subjects. Holt and associates^{20b} have also studied experimental human deficiencies of methionine and of cystine.

While experimental evidence is not available in most cases, it seems clear that the rat is able to synthesize the dispensable amino acids if these are not supplied in the diet. The tissue protein synthesized during growth in such experiments must be assumed to be of a type normal and characteristic of the species, since it is considered axiomatic that "the tissues either form a typical protoplasmic product, or none at all."²¹ In the case of the sulfur-containing amino acids, the evidence seems clear that the dispensable cystine may be synthesized from the essential methionine.²²

The function of the essential amino acids, other than for the construction of new protoplasm, is not clear. Studies of the relation of the essential amino acids to the maintenance of adult animals are not extensive. It seems probable, however, that most of the amino acids which are required for growth will be demonstrated to be essential for the maintenance of adult animals. Methionine is a precursor of cystine, an amino acid important in the molecule of the proteins of epidermal structures and also of certain hormones, particularly insulin, in the molecule of which 12 per cent of cystine is present and no methionine.²³ Methionine also supplies methyl groups for the synthesis of choline, a dietary essential, and of creatine, important for maintenance of muscle function.²⁴ Phenylalanine presumably furnishes the nucleus for the synthesis of thyroxine, the iodine-containing amino acid present in the specialized physiologically active thyroglobulin of the thyroid, and of epinephrine, the endocrine principle

20b. Albanese, A. A.; Holt, L. E., Jr.; Brumback, J. E., Jr.; Kadji, Charlotte N.; Frankston, Jane E., and Wangerin, Dorothy M.: Nitrogen Balance in Experimental Human Deficiencies of Methionine and Cystine, *Proc. Soc. Exper. Biol. & Med.* **59**: 18-20 (Jan.) 1943.

21. Osborne, T. B., and Mendel, L. B.: Amino Acids in Nutrition and Growth, *J. Biol. Chem.* **17**: 325-349, 1914. Quotation is from page 334.

22. Lewis, H. B.: The Significance of the Sulfur-Containing Amino Acids in Metabolism, Harvey Lectures, Baltimore, Williams & Wilkins Company, 1940-1941, series XXXVI, p. 159. Rose, W. C., and Wood, T. R.: The Synthesis of Cystine in Vivo, *J. Biol. Chem.* **141**: 381-389 (Nov.) 1941.

23. Miller, G. L., and du Vigneaud, Vincent: The Cystine Content of Insulin, *J. Biol. Chem.* **118**: 101-110 (March) 1937. du Vigneaud, Vincent; Miller, G. L., and Rodden, C. J.: On the Question of the Presence of Methionine in Insulin, *ibid.* **121**: 631-640 (Dec.) 1939.

24. du Vigneaud, Vincent: Interrelationships Between Choline and Other Methylated Compounds, in *Biological Symposia*, edited by H. B. Lewis, Lancaster, The Jacques Cattell Press, 1941, vol. 5, p. 234. Lewis.²⁵

of the adrenal medulla. Histidine may be decarboxylated to yield histamine, the amine whose biologic role seems demonstrated.²⁵ Arginine is believed to supply the amidine group for the synthesis of creatine.²⁶ Specific functions for the other essential amino acids are yet to be suggested.

Important as these observations concerning the essential nature of certain amino acids are, it should be borne in mind that it is unlikely that physiological economy is to be achieved by the exclusive use of these amino acids as a source of dietary nitrogen. The mixture of amino acids as they occur in the protein of the foodstuffs is still to be regarded as the optimal source of the amino acids required for the synthesis of tissue protein. That it may be desirable to exclude a specific amino acid or acids from the diet of the individual in some definite pathological condition is not improbable but as yet no experimental evidence is available to support such a suggestion.

An important application of the observations that properly chosen mixtures of amino acids may replace proteins in nutrition has been the clinical use of protein hydrolysates, prepared for the most part by enzymatic action on proteins in vitro. These preparations may be administered either orally or parenterally. The utilization of intravenously injected amino acids over a considerable period was first demonstrated by Henriques and Anderson²⁷ in experiments with a goat. The clinical use of such protein hydrolysates has been studied extensively by Elman²⁸ and others.²⁹ Intravenous administration of protein hydrolysates has been shown to be beneficial when feeding by mouth is not

25. Best, C. H., and McHenry, E. W.: Histamine, *Physiol. Rev.* **11**: 371-477 (Oct.) 1931.

26. Bloch, Konrad, and Schoenheimer, Rudolf: The Biological Precursors of Creatine, *J. Biol. Chem.* **138**: 167-194 (March) 1941.

27. Henriques, V., and Anderson, A. C.: Ueber parenterale Ernährung durch intravenöse Injektion, *Ztschr. f. physiol. Chem.* **88**: 357-369, 1913.

28. Elman, Robert: Parenteral Replacement of Protein with the Amino Acid of Hydrolyzed Casein, *Ann. Surg.* **112**: 594-602 (Oct.) 1940. Elman, Robert: Acute Protein Deficiency (Hypoproteinemia) in Surgical Shock, *J. A. M. A.* **120**: 1176-1180 (Dec. 12) 1942.

29. Farr, L. E.: Indications for the Therapeutic Use of Intravenous Amino Acids, *Connecticut M. J.* **5**: 24-27 (Jan.) 1941. Beling, C. A., and Lee, R. E.: Treatment of Hypoproteinemia by Oral Administration of Protein Hydrolysates, *Arch. Surg.* **48**: 735-747 (Nov.) 1941. Altschuler, S. S.; Sahyun, M.; Schneider, Helene, and Satriano, Daniel: Clinical Use of Amino Acids for the Maintenance of Nitrogen Equilibrium, *J. A. M. A.* **121**: 163-167 (Jan. 16) 1943. Abbott, W. E., and Mellors, R. C.: Total Circulating Plasma Proteins in Surgical Patients with Dehydration and Malnutrition: Indications for Intravenous Alimentation with Amino Acids, *Arch. Surg.* **48**: 277 (Feb.) 1943.

possible or is inadvisable. Since hydrolysis destroys the biologic specificity of the native proteins, protein hydrolysates orally administered have proved of value in supplying nitrogen to persons with severe food allergies.³⁰ Whipple and his co-workers have demonstrated that protein hydrolysates may function effectively in the restoration of plasma protein in dogs whose reserve of tissue and plasma proteins have been depleted by bleeding.^{31, 31a} Clinical use of such hydrolysates when plasma is not readily available may become important. The role of amino acids in the formation of hemoglobin has also been the subject of study,^{31a, 31b}

The problem of the amount of protein which is essential or optimal in the diet of man has received much study. Many excellent critical summaries are available.³² Two general methods of approach to this problem have been followed: 1. The endogenous protein metabolism has been determined experimentally, since by many investigators³² the basal or maintenance requirement for protein is considered to be identical with this fraction. 2. In the statistical approach, the quantity of protein in the diet of well nourished middle class racial groups has been estimated. Since these diets are usually not on the level of *luxus* consumption, it is believed that they may afford safe indexes of desirable national nutrition.

It is usually accepted that *luxus* consumption of protein over prolonged periods is of no permanent value to the adult organism, since in contrast to fat and carbohydrate, protein and its building stones, the amino acids, are not stored. This is seen in the state of

30. Hill, L. W.: Amino Acids as a Source of Nitrogen for Allergic Infants, *J. A. M. A.* **116**: 2135-2136 (May 10) 1941.

31. Madden, S. C., and Zeldis, L. J.; Hengerer, A. D.; Miller, L. L.; Rowe, A. P.; Turner, A. P., and Whipple, G. H.: Casein Digests Parenterally Utilized to Form Blood Plasma Protein, *J. Exper. Med.* **73**: 727-743 (June) 1941. Beling and Lee.³⁰ Madden, S. C.; Carter, J. R.; Kattus, A. A.; Miller, L. L., and Whipple, G. H.: Ten Amino Acids Essential for Plasma Protein Production Effective Orally or Intravenously, *J. Exper. Med.* **77**: 277-295 (March) 1943.

31a. Robschey-Robbins, Frieda S.; Miller, L. L., and Whipple, G. H.: Hemoglobin and Plasma Protein. Simultaneous Production During Continued Bleeding as Influenced by Amino Acids, Plasma, Hemoglobin and Digests of Serum, Hemoglobin and Casein, *J. Exper. Med.* **77**: 375-396 (April) 1943.

31b. Robschey-Robbins, Frieda S.: Amino Acids in Hemoglobin Formation, *Federation Proc.* **1**: 219-224 (April) 1943.

32. Terroine, E.: The Protein Component of the Human Diet, *Quart. Bull. Health Organisation, League of Nations* **5**: 427-492 (Sept.) 1936. Leitch, I., and Duckworth, J.: The Determination of the Protein Requirements of Man, *Nutrition Abstr. & Rev.* **7**: 257-267 (Oct.) 1937. Garry and Stiven,³⁰ Morris,³⁰ Cuthbertson,³⁰

nitrogenous equilibrium or balance. If the dietary protein of a normal adult is adequate, the nitrogen of the diet (chiefly protein nitrogen) is equal to the nitrogen of the excreta (mainly the nitrogen of the urine). If to the diet of such a person increased amounts of protein are added, there is a sharp increase in the nitrogenous waste products of the urine (largely urea, derived from protein catabolism), and within a relatively short time nitrogenous equilibrium is again obtained but at a higher level of excretion. If new protein is being synthesized in the body (growth, pregnancy and lactation), the nitrogen excreted is less than that of the diet and the subject is said to be in positive nitrogen balance. When the nitrogen excreted is greater than the dietary nitrogen, a condition of negative balance is obtained. This indicates an inadequate intake of dietary protein or an excessive breakdown of body protein associated with disease.

The level of endogenous nitrogen protein metabolism may be obtained by a consideration of the nitrogen excretion of an adult maintained on a diet high in its content of fat and carbohydrate but containing no protein. Experimentally this has been found to approximate 3 Gm. a day for a man weighing 70 Kg., or about 20 Gm. of protein.³³ There is, however, evidence that to provide a safe allowance for health, protein in excess of the requirements for maintenance is essential. It is argued that excessive consumption of protein imposes a burden on the organism and is likely to be harmful. The proponents of the high protein diet, on the other hand, argue that a surplus of protein may have a beneficial effect on health and well-being and cite studies of racial groups which indicate that physical efficiency and health can be related directly to the intake of protein and particularly of animal protein. The high protein diet of the Eskimo, in which the protein is obtained almost entirely from meat, does not appear to have resulted in a high incidence of renal disease in this group.³⁴ The careful studies of the metabolism of 2 Arctic explorers who lived for a year in the temperate zone on a diet of meat only are of particular

33. Martin, C. J., and Robinson, R.: *The Minimum Nitrogen Expenditure of Man and the Biologic Value of the Various Proteins for Human Nutrition*, *Biochem. J.* 16: 407-447, 1922. Terroine.³⁵

34. Rabinowitch, I. M.: *Clinical and Other Observations on Canadian Eskimos in the Eastern Arctic*, *Canad. M. A. J.* 34: 487-501 (May) 1936.

interest.³⁵ It must be remembered, however, that in studies of human populations the protein element is only one of many factors in health and that it is difficult to assess the role of dietary protein alone without many greatly extended studies.³⁶

Outstanding among the pathologic conditions which have been associated with prolonged ingestion of a diet inadequate in its protein content is nutritional edema (known also as war or starvation edema), which has been observed clinically in Europe, in the Orient and in the United States and can be produced experimentally in animals maintained on a low protein diet.³⁷ The continued ingestion of the low protein diet results in low levels of plasma protein (particularly the albumin fraction), and the resultant lowering of the "effective" osmotic pressure of the plasma is believed to be the cause of the edema.

This discussion indicates the desirability of caution in the selection of a standard protein level for national nutrition. Extremes are to be avoided. One of the first attempts to assess the desirable level of protein of the diet by the statistical approach was that of Voit. In a study of the diets of the average laborer in Germany a daily consumption of 118 Gm. of protein was observed. So great was the prestige of Voit that this standard allowance of dietary protein was accepted without serious challenge for a quarter of a century. Chittenden of Yale and Hindhede of Copenhagen in the early part of the present century held that the "Voit standard" diet supplied an excessive amount of protein and that a lower level was desirable. It is not necessary to enter into the details of the controversy between the advocates of the low and high protein diet, a controversy which is excellently and impartially presented in the classic text of Graham Lusk.³⁸ Sherman, after a careful consideration of the acceptable balance experi-

35. McClellan, W. S., and Du Bois, E. F.: *Clinical Calorimetry*: XLV. Prolonged Meat Diets with a Study of Kidney Function and Ketosis, *J. Biol. Chem.* **87**: 651-668 (July) 1930. McClellan, W. S.; Rupp, V. R., and Toscani, V.: XLVI. Prolonged Meat Diets with a Study of the Metabolism of Nitrogen, Calcium and Phosphorus, *ibid.* **87**: 669-680 (July) 1930.

36. Cuthbertson, D. P.: *Quality and Quantity of Protein in Relation to Human Health and Disease*, *Nutrition Abstr. & Rev.* **10**: 1-20 (July) 1940.

37. Youmans, J. B.: *Nutritional Deficiencies, Diagnosis and Treatment*, Philadelphia, J. B. Lippincott Company, 1941, p. 231.

38. Lusk, Graham: *The Elements of the Science of Nutrition*, ed. 4, Philadelphia and London, W. B. Saunders Company, 1928, p. 448.

ments with human beings, in which nitrogen equilibrium was established at low levels of dietary protein, concluded that "a standard allowance of 1 Gm. of protein per kilo of body weight per day appears, therefore, to provide a margin of safety of 50 to 100 per cent as far as requirements of adult maintenance are concerned."³⁹ This standard for adult maintenance has been accepted almost universally, while the need for larger amounts of protein in diets of growing children and of pregnant and lactating women is clearly recognized. The recently adopted standards for national nutrition, as proposed by the Food and Nutrition Board of the National Research Council, provide for 70 Gm. of protein a day in the diet of a man weighing 70 Kg. and 60 Gm. of dietary protein for a woman weighing 56 Kg.

Estimates of the increased requirements for protein during pregnancy and lactation vary greatly.⁴⁰ The protein requirement per kilogram of body weight is high in infancy and decreases as growth occurs until after puberty, when the adult requirements only are necessary. The desirable amount of dietary protein is estimated to vary from 4 Gm. per kilogram a day at 1 to 3 years to 2 Gm. at 17 to 18 years. The necessity of protein with high biologic value, such as the proteins of milk, during the period of active growth can hardly be overemphasized. That increased muscular activity necessitates a larger intake of protein is as yet unproved. Traditionally the diet of highly trained athletes and of laborers engaged in hard work, whose calorific requirements are high, contains much meat and supplies large amounts of protein.⁴⁰

The preceding discussion has been concerned with the quantitative aspects of the protein requirements of man. That the dietary protein will be derived from a wide variety of foodstuffs of both animal and vegetable origin is assumed. In the United States, it is estimated that animal protein makes up at least 50 per cent of the usual diet. If the variety of foodstuffs is limited, care must be exercised in the selection of

39. Sherman, H. C.; Gillett, L. H., and Osterberg, E.: Protein Requirement of Maintenance in Man and the Nutritive Efficiency of Bread Protein, *J. Biol. Chem.* **41**: 97-109 (Jan.) 1920.

40. Garry, R. C., and Stiven, D.: A Review of Recent Work on Dietary Requirements in Pregnancy and Lactation, with an Attempt to Assess Human Requirements, *Nutrition Abstr. & Rev.* **5**: 855-887 (April) 1936. Morris, Samuel: The Protein Requirements of Lactation, *ibid.* **3**: 273-280 (Oct.) 1936.

protein. The chief consideration in the choice of protein must be the furnishing of the essential amino acids to be made available to the tissues by digestion. Since the optimal mixture of the essential amino acids for the nutrition of man is not yet known, the diet must supply all the known essential amino acids in liberal amounts. Animal proteins usually have a greater biologic value than do the proteins of vegetable origin. Thus zein, one of the proteins of the maize kernel, contains no lysine or tryptophan, two important essential amino acids. When the diet is derived exclusively from plant materials, more protein must be eaten. A notable exception is gelatin. This protein, a product of food technology and derived from collagen, completely lacks at least two essential amino acids, valine and tryptophan, and contains little tyrosine and cystine, amino acids which, while not essential, may be important in nutrition. Gelatin supplies a mixture of amino acids, which is inadequate if used as the sole or chief source of these tissue-building stones. The recent claims for the superior food value of gelatin require further and more careful study.⁴¹ The excellent quality of the mixture of proteins present in milk is notable.

Carbohydrates spare body protein. The breakdown of body protein is significantly increased if the supply of the energy-producing foods and particularly of carbohydrates is not ample. The consideration of the total calorific value of the diet is of special importance when the diet is low in its protein content, as are certain diets prescribed for therapeutic purposes. Diets of high calorific content usually contain liberal or large amounts of protein.

It is known that in the case of certain essential elements present in food (notably the vitamins) the nutritive value may be influenced by preservation, processing and cooking.⁴² Thus the nutritive values of a natural foodstuff as determined by chemical analysis may not be a safe guide to its value when prepared for consumption. Since foodstuffs which are important sources of protein are seldom consumed in the raw state, possible changes due to heat must be considered. Even milk in present day practice is usually subjected to the

41. The Nutritional Significance of Gelatin, Report of the Council on Foods, J. A. M. A. 107: 2132-2133 (Dec. 26) 1936.

42. Kohman, E. P.: The Preservation of the Nutritive Value of Foods in Processing, J. A. M. A., to be published; article XV in this series.

mild heat of pasteurization. The evidence in the case of proteins is conflicting. The biologic value of the protein of certain legumes is believed to be increased by cooking, while the nutritive value of some other proteins (meat, casein and milk products) appears to be lowered by heat.⁴³ A detailed discussion is not possible here. Whether such changes are sufficiently extensive to be of practical significance remains to be determined.

No discussion of recent developments in protein metabolism can neglect the mention of the experiments of Schoenheimer in which isotopic nitrogen (N^{15}) has been used as a marker. These experiments indicate that a "rapid and continuous chemical regeneration of the cell proteins is a general characteristic of living matter," but despite this striking and continuous chemical activity of the organ proteins it is believed that these processes "lead to no final quantitative or qualitative changes" in the composition of the tissues.⁴⁴ This is in confirmation of the older belief in the constancy of composition of the structural elements of protoplasm. While the observations of Schoenheimer and his group are of great physiologic significance, it is not believed that at present they suggest any changes in the current practices of dietetics so far as concerns protein.

Karl Thomas in 1929 thus summarized the unsolved problems of the biologic value of protein:⁴⁵ "What we need to know is: 1. Which amino acids must be present in the food, 2. How much we require of each, 3. And to what purpose." Today, after more than a decade of intense interest and research in protein metabolism, these questions still epitomize the problem of the role of proteins in nutrition. When they can be answered exactly, the role of protein in the diet will be known, and one will be able to determine the dietary value of every mixture of proteins in natural foodstuffs.

43. Johnson, L. Margaret; Parsons, Helen T., and Steenbock, Harry: The Effect of Heat and Solvents on the Nutritive Value of Soy Bean Protein, *J. Nutrition* 18: 423-434 (Oct.) 1939.

44. Schoenheimer, Rudolf, and Rittenberg, D.: The Study of Intermediary Metabolism of Animals with the Aid of Isotopes, *Physiol. Rev.* 20: 218-248 (April) 1940. Schoenheimer, Rudolf, and Ratner, S.: The Metabolism of Proteins and Amino Acids, *Ann. Rev. Biochem.* 10: 197-220, 1941.

45. Thomas, Karl: Biological Values and the Behavior of Food and Tissue Protein, *J. Nutrition* 9: 419-435 (March) 1930.

CHAPTER III

ROLE OF FAT IN THE DIET

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Fat is used biologically mainly as a source of energy and as a constituent of the body tissues. It has minor functions, such as carrying important accessory substances. Weight for weight, fat supplies about twice the energy of the other staple organic foods, carbohydrate and protein. It is an essential in the structure and functions of all tissues and especially of the brain and nerves. The natural fats contain many of the vitamins which are necessary for the growth, maintenance and well-being of animals and probably plants as well. Fats serve passively as heat insulation under the skin, as padding to keep the bodily organs and blood vessels and nerves in place, and for rounding out the angular contours of the bodily structure. They constitute the most important form of stored energy for tiding the animal over through periods of food scarcity and for transmitting to the offspring, as milk or egg, food material to serve until the young animal can forage for itself. Most fats are readily synthesized by animals from other foods but there are certain important exceptions, fatty acids, which must be supplied in the food and the lack of which produces the fat deficiency disease. Fat is thus an important source of energy both immediate and remote. As ordinarily used, mixed with considerable other food, it is completely and easily digested and used. When used alone or when it is the main food constituent of the diet, it is less well used and may cause important disturbances in the organism.

The proper understanding of the part taken by fat in the life processes of animals requires a consideration of the chemical nature of fat and its various related substances and the changes which they undergo in their use by animals. The characteristic constituents of the group comprising the food and body fats and related substances (ordinarily grouped under the name of lipids) are the fatty acids. These are monobasic

straight chain acids, two to twenty-four or more carbon atoms in length, some of them with from one to six unconjugated double bonds per molecule. The commonest ones in both food fat and body stores are palmitic ($C_{16}H_{32}O_2$), oleic ($C_{18}H_{34}O_2$) and stearic ($C_{18}H_{36}O_2$) acids with linolic ($C_{18}H_{32}O_2$) and palmitoleic ($C_{16}H_{30}O_2$) close seconds and a variety of others mostly confined to some tissue or fluid in the organism. Some of these are butyric ($C_4H_8O_2$) found in milk fat, arachidonic ($C_{20}H_{32}O_2$) in brain, liver, muscle and other tissues, lignoceric ($C_{24}H_{48}O_2$) in brain and nerve, and cerebronic ($C_{24}H_{46}O_3$), α -hydroxylignoceric,¹ in brain. For the complete list and for other detailed information regarding classification of the fatty acids and their compounds, the reader is referred to the numerous good textbooks of biochemistry.

Melting points of the fatty acids depend on the length of chain and on the number of double bonds. The longer the chain the higher the melting point, while double bonds lower the melting point. Thus stearic acid ($C_{18}H_{36}O_2$), a long chain saturated acid, has a melting point of 69.5 C., while lauric acid ($C_{12}H_{24}O_2$) melts at 43.6 C. and oleic acid ($C_{18}H_{34}O_2$), corresponding to stearic acid but with one double bond, has a melting point of 14 C., the double bond lowering the melting point about 55 degrees C. Since the melting points of the constituent fatty acids determine the melting points of the fats and since the stored fat must be kept fluid while the animal is alive, there is often a careful adjustment of the fatty acid mixture in the fat stores.

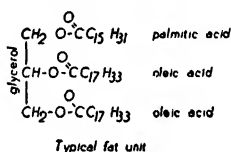
The fatty acids exist in various types of combination in the animal body. Most common of these is that of the fats, also called neutral fats, which are triglycerides of the fatty acids. These are compounds in which the trihydroxy alcohol glycerin is combined in ester combination with three fatty acids. In nature these three fatty acids are rarely the same. Often three different fatty acids are found and in general (Hil-ditch's rule)² there will be as great a variety of fatty acids in the triglyceride molecule as are available to the animal at the time the fat was synthesized. The

1. Klenk, E.: Ueber die Cerebronsäure, *Ztschr. f. physiol. Chem.* 179: 312 (Dec.) 1928.

2. Longenecker, H. E.: Composition and Structural Characteristics of Glycerides in Relation to Classification and Environment, *Chem. Rev.* 29: 201 (Oct.) 1941.

selection is also controlled by the necessity of a balance between saturated and unsaturated acids or perhaps by the requirement that the completed triglyceride have a melting point not far from the body temperature of the animal. The fact that these esters as well as the fatty acids themselves generally have two and sometimes more melting points some distance apart and that they can be kept in a greatly supercooled condition for long periods of time are facts which require something more complicated than the simple triester type of formula. Evidence points to the occurrence of these esters in several polymorphic forms.³

The formula for a typical fat unit is



which would be called palmitodiolein. The naturally occurring fats generally contain several varieties of such units.

In all living organisms fatty acids occur in several types of combination in addition to that in the fats, and, since these compounds are now believed to be either stages in the progress of the fats through the processes of metabolism or important constituents of the living cells, it is necessary to include them in the discussion. These compounds include the phosphorylated fats or phospholipids, found everywhere in animal tissues, the cerebrosides, which contain a sugar in fatty acid combination, found in the brain and nerves, and cholesterol, which always occurs along with the fats, generally free but sometimes in ester combination with the fatty acids, as in the cholesterol esters of blood plasma.

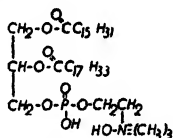
PHOSPHOLIPIDS

The phospholipids or phosphorylated fats call for an extended discussion, since they are connected with the fatty acids in several stages of their metabolism and are important cellular constituents. Phosphoric acid

3. Grüntzig, W.: Ueber die Schmelzpunktsalternation der höheren, einsäurigen Triglyzeride, Ztschr. f. anorg. Chem. **240**: 313 (March 7) 1939.

has long been recognized as one of the necessary food constituents of both plants and animals, but only recently has light been thrown on just why it is so necessary. Thus the part which it takes in the metabolism of the carbohydrates has been well worked out, and, although the picture is incomplete in some details, enough has been shown to indicate that the phosphoric acid takes part in most of the stages of carbohydrate metabolism. In fat metabolism only the first stages of phosphoric participation are known. There are three main types of phosphorylated fats, the first two, lecithin and cephalin, being very similar in composition while the third one, sphingomyelin, is quite different. Since different fatty acids enter into each of these compounds, there are several members of each group.

Lecithin is believed to have a composition represented by the formula



Palmito-oleo-lecithin

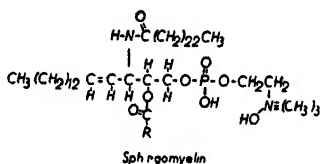
This would be called palmito-oleo-lecithin. As may be seen, it is an ordinary fat with one of the fatty acids on the glycerin molecule replaced by phosphoric acid in combination with the base choline.

Cephalin is believed to differ from lecithin only in the nature of the base in combination with the phosphoric acid, which in this case is either aminoethyl alcohol ($\text{CH}_2\text{OH}.\text{CH}_2.\text{NH}_2$) or its carboxylated form, serine. There are two forms of both lecithin and cephalin, the α form in which the phosphoric group is on the terminal carbon of the glycerin and the β form in which it is on the middle carbon. Both forms occur in tissues, and it is significant that α -lecithin and β -cephalin disappear during starvation, while the β -lecithin and α -cephalin persist.⁴

The third phospholipid, sphingomyelin, as the derivation of the name indicates, is still the "mystery" sub-

4. MacLachlan, P. L.; Hodge, H. C.; Bloor, W. R.; Welch, E. A.; Truax, F. L., and Taylor, J. D.: *Lipids of the Fasting Mouse: II. The Fat to Water Relation and the Fractionation of the Liver Phospholipids*, *J. Biol. Chem.* 143:473 (Apr.) 1942.

stance. It is found mainly in brain and nerve and in small amounts in other tissues including the blood. The present accepted formula is



It would be called lignoceryl-sphingosine-phosphoric-acid-choline-ester. It is made up of the two bases sphingosine, which is an unsaturated C_{18} chain with one amino and two hydroxy groups, and choline, both of which are united to the phosphoric acid by ester linkages. It contains one fatty acid, ordinarily the saturated lignoceric ($C_{24}H_{48}O_2$), united with the sphingosine as an acid amide, and often another fatty acid united by an ester linkage with the other hydroxyl group. The fact that sphingomyelin sometimes contains two fatty acids and sometimes only one ⁵ indicates that it may be of importance in the transport of fatty acids. The fact that the fatty acid in ester linkage may be detached by alkaline hydrolysis or by lipases, while the amide linked fatty acid is not affected, is of unknown significance. Fragments of sphingomyelin, e. g. lignoceryl sphingosine, were found by Thudichum in brain and later by others in liver,⁶ and sphingosine phosphoric acid choline has been reported in kidney.

A significant difference between the phospholipids and the fats is that the phospholipids contain groups which have a strong affinity for water (phosphoric acid and bases) which render the phospholipids miscible with if not actually soluble in water. The phospholipids thereby provide a physical link between the water insoluble fats and cholesterol on the one hand and the tissues and fluids of the animal body which are either water soluble or mix readily with water. Phospholipids and cholesterol are found in cell walls and mem-

5. Reichel, M., and Thannhauser, S. J.: Studies on Animal Lipids: XVII. The Synthesis of Lignoceryl sphingosine Fatty Acid Esters (Sphingosine Fats) and Sphingosine Amides (Ceramides), J. Biol. Chem. 135:15 (Aug.) 1940.

6. Thannhauser, S. J., and Fränkel, E.: Ueber das Lignocerylsphingosine: II. Zur Kenntnis des sogenannten Unverseifbaren der Säugtierleber, *Ztschr. f. physiol. Chem.* **303**, 183, 1931.

branes and, because they are intermediate in properties between the water insoluble fats and the watery environment, undoubtedly serve to regulate the passage of water and water soluble material as well as to facilitate the passage of fat in and out of such cells as those of the intestinal epithelium, the liver cells and the cells of the fat stores. In the intestine this passage appears to be brought about by processes of hydrolysis and resynthesis in which the phospholipids take part, and the same may be true in the case of other cells. One of the impressive phenomena of cellular processes in general is the ease with which hydrolysis and recombination take place. Lecithin and sphingomyelin are nearly neutral substances, for although they contain strong acidic and basic groups these appear to be internally compensated either by union of the opposing groups with loss of water or by the zwitterion form. Cephalin, on the other hand, may be titrated as a monobasic acid, since the bases which it contains, aminoethyl alcohol or serine, are too weak to interfere with the titration of the strongly acidic third hydrogen of the phosphoric acid. Its acidic character gives it the power to combine with the basic groups of proteins and with metals, a fact which may explain its importance in such processes as blood coagulation. The fact that cephalin sometimes contains serine and sometimes the decarboxylated base (aminoethyl alcohol) may explain the fact that when it is too highly purified it is no longer effective in blood coagulation.

Lecithin and cephalin exist in living organisms almost entirely in the "complete" form, i. e., have their full complement of fatty acids and base. Under certain circumstances they may lose one fatty acid, becoming lysolecithins and lysocephalins, or they may lose the base, becoming phosphatidic acids. Lysolecithin and lysocephalin are highly dangerous substances because, as their names indicate, they bring about extensive lysis and destruction not only of red blood cells but of tissue cells as well. The increased affinity for water which the loss of one fatty acid confers makes them excellent wetting agents with the result that, entering the cell wall, they upset the water balance between cell and fluid, causing swelling and bursting of the cells. Much of the destructive power of some snake venoms is due

to the fact that they contain an enzyme which produces these lyso compounds. Phosphatidic acid is not known to occur in animals but is found in plant leaves.⁷

Sphingomyelin may take on an extra fatty acid in ester combination at its second hydroxyl group⁸ and, since this acid has been found to be one of the common fatty acids (palmitic), it seems likely that sphingomyelin takes a more active part than has been supposed in the processes of fat metabolism.

Lecithin and cephalin in the living organism appear to be very labile substances, exchanging their fatty acids and their phosphoric acid with similar materials coming in with the food. The exchange of fatty acids takes place rapidly in the intestinal epithelium; in fact, it appears that this passage of fatty acids into and out of the framework of the epithelial phospholipids is the method or an important method of fatty acid absorption. Phosphoric acid of the food also has been shown to exchange with the phosphoric acid of the cellular phospholipid. These exchanges have been satisfactorily demonstrated by the modern use of labeled or tagged fatty acids and phosphorus as food. The fatty acids used were those of cod liver oil and elaidin by Sinclair,⁹ the latter prepared by treatment of ordinary olive oil with nitrous acid. The phosphorus used was the P³² isotope, which is radioactive and has been used as a tracer substance in fat metabolism by several investigators, notably Chaikoff and his associates,¹⁰ and in this laboratory by Haven.¹¹ Other labeled fatty acids which are satisfactory are those containing conjugated double bonds, either natural as in tung oil or artificial

7. Channon, H. J., and Chibnall, A. C.: The Ether Soluble Substances of Cabbage Leaf Cytoplasm: IV. Further Observations on Diglyceridephosphoric Acid, *Biochem. J.* **21**: 1112, 1927.

8. Thannhauser, S. J., and Reichel, M.: Studies on Animal Lipids: XVI. The Occurrence of Sphingomyelin as a Mixture of Sphingomyelin, Fatty Acid Ester and Free Sphingomyelin, Demonstrated by Enzymatic Hydrolysis and Mild Saponification, *J. Biol. Chem.* **135**: 1 (Aug.) 1940.

9. Sinclair, R. G.: The Metabolism of the Phospholipids: VIII. The Passage of Elaidic Acid into Tissue Phospholipids: Evidence of the Intermediary Role of Liver Phospholipid in Fat Metabolism, *J. Biol. Chem.* **111**: 515 (Oct.) 1935.

10. Perlman, I.; Ruben, S., and Chaikoff, I. L.: Radioactive Phosphorus as an Indicator of Phospholipid Metabolism: I. The Rate of Formation and Destruction of Phospholipids in the Fasting Rat, *J. Biol. Chem.* **122**: 169 (Dec.) 1937.

11. Haven, F. L.: The Rate of Turnover of the Lecithins and Cephalins of Carcinoma 256 as Measured by Radioactive Phosphorus, *J. Nat. Cancer Inst.* **1**: 205 (Oct.) 1940.

as produced by prolonged saponification of corn oil. These have been used by Burr and his associates.¹²

Rapid exchanges were found also in the lipids of liver in the case of both fatty acids and phosphoric acid and considerably less rapid in muscle and most other tissues. Brain, nerve tissue and testicle have a very slow exchange. The significance of these exchanges in the tissues is not yet understood, but they emphasize the fact that the fatty acid compounds in tissues are quite labile, giving up or taking on new units according to the supply from the food. This conception of ever labile compounds has been found to hold also for the body proteins¹³ and is compatible with the fact that chemical processes in the animal body must be carried on without the usual laboratory aids in bringing about chemical changes, i. e., heat, strong acids, bases or other strong reagents. The warm blooded animal body is a well regulated thermostat kept at about 37° C. and likely to be severely damaged by temperatures much below and especially much above that "normal" level. The body fluids are very nearly neutral in reaction and are similarly regulated about the neutral point. Close regulation extends also to concentration of the various bodily constituents and to the balance between fluids inside and outside the cell. Consequently the body components must be such as can undergo fundamental transformations readily under narrowly limited conditions.

Although free exchange has been established of the various constituents of the phospholipids (at least of lecithin and cephalin) with the incoming ones from the food, certain preferences have been established. Thus Sinclair¹⁴ found that, although the fatty acid constituents of the phospholipids of the intestinal mucosa, liver and muscles changed in response to the fatty acids of the food, the more highly unsaturated fatty acids of cod liver oil were taken up more rapidly and retained more tenaciously than other fatty acids.

12. Barnes, R. H.; Miller, E. S., and Burr, G. O.: The Absorption and Transport of Fatty Acids Across the Intestinal Mucosa, *J. Biol. Chem.* **140**: 233 (July) 1941.

13. Schoenheimer, Rudolf; Ratner, S., and Rittenberg, D.: Studies in Protein Metabolism: X. The Metabolic Activity of Body Proteins Investigated with 1(—)-Leucine Containing Two Isotopes, *J. Biol. Chem.* **130**: 703 (Oct.) 1939.

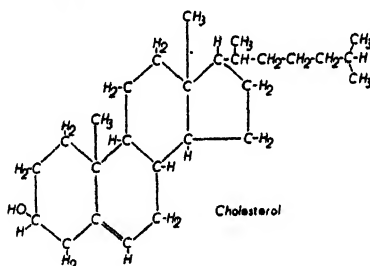
14. Sinclair, R. G.: The Metabolism of the Phospholipids: V. The Relationship Between the Amount of Fat Ingested and the Degree of Unsaturation of the Phospholipids and Neutral Fat in the Tissues of the Rat, *J. Biol. Chem.* **96**: 103 (April) 1932.

The special desirability of highly unsaturated acids as phospholipid constituents fits in with other findings regarding the tissue phospholipids—their ready oxidizability in air and hence the difficulty of preparing them in even approximately pure form.

The need of the organism for the more highly unsaturated fatty acids finds expression in the fat deficiency disease which develops in experimental animals as the result of the lack of certain necessary fatty acids in the diet¹⁵ and is cured by the addition to the diet of these acids or acids from which the essential ones can be made. MacLean and her associates¹⁶ have suggested that the essential unsaturated acid is arachidonic ($C_{20}H_{32}O_2$), a four double bond acid which the organism can manufacture from those acids, linoleic and linolenic, which cure the fat deficiency disease.

CHOLESTEROL AND CHOLESTEROL ESTERS

Cholesterol ($C_{27}H_{46}OH$) has the formula shown.



It is a member of the large group known as sterols and is part of a still larger group known as the steroids or sterids. Also members of this group and chemically closely related to cholesterol are the bile acids, the sex hormones and substances occurring as glucosides in such compounds as digitalis and toad poisons. Whether cholesterol can be changed into these important substances or has any physiologic relation to them has not been shown. Cholesterol is connected with the fats in their role in the animal organism because it

15. Burr, G. O., and Burr, Mildred M.: A New Deficiency Disease Produced by the Rigid Exclusion of Fat from the Diet, *J. Biol. Chem.* **83**: 345 (May) 1929.

16. Hume, Eleanor M.; Nunn, L. C. A.; Smedley-MacLean, Ida, and Smith, Hannah H.: Fat Deficiency Disease of Rats. The Relative Curative Potencies of Methyl Linoleate and Methyl Arachidonate with a Note on the Action of the Methyl Esters of Fatty Acids from Cod Liver Oil, *Biochem. J.* **34**: 879 (June) 1940.

always occurs along with them and combines with the fatty acids to form the cholesterol esters. The cholesterol esters occur normally in notable amounts only in blood plasma and the adrenal cortex, but in abnormal conditions they are found in deposits in various parts of the animal body—in the liver, in fatty livers especially when caused by cholesterol feedings, in the walls of diseased arteries either as mushy deposits (atherosclerosis) or in the actually hardened arteries¹⁷ and in gallstones. Cholesterol and cholesterol esters are among the lipids present in the deposits of Niemann-Pick and Schüller-Christian diseases and in the blood and skin and joint nodules of essential hypercholesterolemia. Whether the cholesterol esters of these deposits represent normal stages in the metabolism of the fats or whether they represent a mechanism for the disposal of cholesterol or unusable fatty acids remains unsettled.

The fact that the cholesterol esters of the blood plasma constitute from 60 to 70 per cent of the total plasma cholesterol and the fact that the cholesterol absorbed through the intestine is esterified with the absorbed fatty acids to about the same extent¹⁸ indicate that it is concerned with the transport if not the metabolism of the fatty acids. Recent work¹⁹ as well as older work²⁰ indicates that the fatty acids in combination with the cholesterol are relatively highly unsaturated (average about two double bonds) which leads to the belief that the cholesterol combination has to do mainly with the more unsaturated acids. The presence of cholesterol esterases in blood and tissues is the basis for Sperry and Stoyanoff's²¹ conception that, since cholesterol esters exist in the blood but not in normal tissues, these enzymes are responsible both for the cholesterol-cholesterol ester equilibrium in the blood and also for the breaking up of the ester in its passage into the tissues.

17. Schönheimer, R.: Zur Chemie der gesunden und der atherosklerotischen Aorta: I. Ueber die quantitativen Verhältnisse des Cholesterins und der Cholesterinester, *Ztschr. f. physiol. Chem.* **160**: 61 (Oct.) 1926.

18. Mueller, J. H.: The Assimilation of Cholesterol and Its Esters, *J. Biol. Chem.* **22**: 1, 1915.

19. Kelsey, F. E., and Longenecker, H. E.: Distribution and Characterization of Beef Plasma Fatty Acids, *J. Biol. Chem.* **139**: 727 (June) 1941.

20. Bloor, W. R.: The Fatty Acids of Blood Plasma: II. The Distribution of the Unsaturated Acids, *J. Biol. Chem.* **59**: 543 (April) 1924.

21. Sperry, W. M., and Stoyanoff, V. A.: The Enzymatic Synthesis and Hydrolysis of Cholesterol Esters in Blood Serum, *J. Biol. Chem.* **126**: 77 (Nov.) 1938.

Animals vary a good deal in their ability to absorb and metabolize cholesterol. Herbivorous animals such as the rabbit absorb it slowly and, having absorbed it, have difficulty in disposing of it. In these animals it raises the blood cholesterol and is deposited in characteristic fashion in arterial walls and other places. In omnivorous or carnivorous animals such as the human being and the dog, moderate feeding of cholesterol has no effect on the blood cholesterol nor has it been shown to have any effect on the arterial walls. Gallstone formation has also been shown to be independent of the cholesterol level in the diet. The reason for the lack of effect of dietary cholesterol in omnivorous and carnivorous animals lies in their ability to excrete the excess by way of the intestine. Animals can oxidize cholesterol but slowly. Normally the excretory mechanism is adequate to keep the body in balance as regards cholesterol, but under some circumstances it can be overloaded, with the result that the level of blood cholesterol rises. It has been shown that animals can manufacture cholesterol as needed from compounds of relatively small molecular size.²²

Cholesterol is confined to the animal kingdom. In plants and bacteria there are other but closely related sterols which presumably have a similar function in their life processes. All available evidence indicates that animals cannot use these sterols in place of cholesterol, in fact cannot absorb them from the alimentary tract.

With the exception of the adrenals the cholesterol is normally present in the cells and tissues almost entirely in the free form, while in the blood plasma it is about two-thirds combined with fatty acids as esters. Various figures are available regarding the content of cholesterol in normal human blood, the differences being due to a number of causes. Differences in analytic method will explain some of the divergence: for example digitonin precipitation method always gives lower results than the colorimetric method based on the Liebermann-Burchard reaction. Since even the digitonin method is not specific for cholesterol, it seems likely that true cholesterol values have not yet been found. The relative values reported are, however, probably as useful for most purposes as absolute values.

22. Schoenheimer, R., and Breusch, F.: *Synthesis and Destruction of Cholesterol in the Organism*, J. Biol. Chem. **103**: 439 (Dec.) 1933.

Diet undoubtedly plays a considerable role in blood cholesterol values, especially in herbivorous animals, although moderate effects are demonstrable in omnivorous and carnivorous animals as well.

The thyroid secretion appears to have an effect on the blood cholesterol level. Hyperthyroidism lowers blood cholesterol as though the more intense metabolism in this condition resulted in a more complete combustion, while in hypothyroidism the blood cholesterol level is higher. Since all workers have not obtained pronounced differences, the thyroid effect should be regarded as probable but not invariable.

In the variety of nephritis commonly called nephrosis, the blood cholesterol values may reach very high levels, five or six times the normal, and are accompanied by fatty (cholesterol ester) deposits in the kidneys. The reason for the high values is unknown.

In diabetes before the insulin era cholesterol and fat values in the blood were often very high, but with insulin treatment and inclusion of carbohydrate in the diet these high values are exceptional. The earlier values were undoubtedly due to the unbalanced, excessively high fat diet.

Essential hypercholesterolemia in human beings appears to be analogous to the state of affairs found in normal rabbits—a very low ability to destroy or excrete cholesterol. The result is that the cholesterol of animal food accumulates in the blood, resulting in excessive values and in depositions of cholesterol similar to the tophi of gout in various places in the body such as the joints and tendons. The symptoms are relieved by giving the patient a vegetable diet (plant sterols not being absorbed), but the disappearance of cholesterol from the nodules is a very slow process.

Cholesterol, mostly in the free form, is found in all bodily tissues, being especially abundant in the adrenals (1.5 per cent, mostly as ester), brain (1 to 1.5 per cent, all free), liver (0.3 per cent) and blood (about 0.2 per cent, two thirds as ester). The cholesterol content of muscle varies with the type of muscle, with the species and with activity. Smooth muscle has the highest content (0.18 to 0.2 per cent moist weight), ventricle muscle (0.14 to 0.2 per cent moist weight) and skeletal (0.07 to 0.09 per cent moist weight).

Hen's egg yolk contains about 1.5 per cent of cholesterol, which would amount to about 0.3 Gm. per egg. Milk contains about 0.02 per cent, amounting to about 0.2 Gm. per quart.

The human being loses by the feces about 1 Gm. of sterol daily, most of which arises in the food either as cholesterol in animal food or as unabsorbed sterols in the vegetable part of the diet.

In most body tissues and fluids there is a well defined balance or ratio between the phospholipid and cholesterol. This ratio varies for different tissues but is fairly constant and characteristic for a single tissue.

In the accompanying table the phospholipid content and the phospholipid/cholesterol ratios are arranged in the order of magnitude: As may be seen, there is

Phospholipid/Cholesterol Ratios

Phospholipid Content % Moist Weight	Phospholipid/Cholesterol Ratio
Brain 4.0	Liver 18
Liver 3.0	Voluntary muscle..... 16
Heart 1.8	Heart 16
Kidney 1.4	Kidney 11
Lung 1.2	Lung 6
Serum 0.2	Serum 2.5
Voluntary muscle..... 0.5-1.0	Brain 2.5

almost a reversal in the relative position of the brain and the muscle in the two columns of the table. Brain, which has the highest phospholipid, has the lowest phospholipid/cholesterol ratio, owing to its high cholesterol content, while voluntary muscle, which has the lowest phospholipid content, has nearly the highest phospholipid/cholesterol ratio, owing to its still lower cholesterol content. The position of the other items in the table is practically the same in the two columns. Among the muscles the ratios for skeletal muscle and heart are the same (14 to 16), while for smooth muscle the ratio is 4, owing to the much higher content of cholesterol, the phospholipid value being about the same as in skeletal muscle. The high cholesterol is thought to be related to the automatic character of the muscle. Smooth muscle contracts regularly independently of external nervous stimuli. Heart muscle also contracts automatically and has a high cholesterol content, but in this case the high cholesterol is balanced by a corre-

spondingly high phospholipid content, so that the ratio remains high. Since nervous tissue is present in muscle and contains both phospholipid and cholesterol, it would be desirable to know the extent of its contribution to the phospholipid and cholesterol of the muscle. Up to the present, no means for such a study has been available. There may be some significance in the fact that in smooth muscle, which is spontaneously active, there is nearly the same phospholipid/cholesterol ratio as in brain.

It may be noted here that creatine phosphorus (phosphocreatine) and lipid phosphorus (phospholipid) appear to be in inverse relationship in heart and skeletal muscle. Creatin phosphorus in heart is about 6 mg. per hundred grams with lipid phosphorus about 80 mg. per hundred grams, while in skeletal muscle the creatine phosphorus is about 60 mg. per hundred grams and the lipid phosphorus about 30 mg. per hundred grams. As is well known, the phosphocreatine of heart muscle must be promptly renewed if the muscle is to continue active, while skeletal muscle can work for a relatively long time before its phosphocreatine is exhausted. A relation between the high phospholipid content of heart muscle and its low phosphocreatine seems likely, and it is a reasonable assumption that the phospholipid is a readily available source of energy for the renewal of the phosphocreatine and perhaps of supply of phosphorus for the compound.

FAT METABOLISM

An understanding of the way in which fat is dealt with in the body is necessary for determining its function in the animal economy. The animal body is about three-fourths water, and practically all reactions which go on in life take place in water solution or in the presence of water. Solubility or miscibility in water is a basic requirement for utilization. Fat and its main constituent, the fatty acids, are insoluble in water, and various devices are employed to make them useful in the watery environment.

The fat entering the organism as food is, like all other foods, first broken up into its constituent parts, the fatty acids and glycerol. This process, hydrolysis, is brought about by enzymes (lipases) supplied mainly in the pancreatic juice. The lipases are in water solu-

tion and, since water does not penetrate fat, the action can take place only at the surface of the fat particles. It would therefore be slow. The devices employed to bring the splitting time within the limits allowed for digestion (about four hours) are first to increase greatly the surface, which is done by emulsification. Emulsification is accomplished by the help of a small amount of soap formed by interaction of the alkali of the pancreatic secretion with free fatty acid always present in fat. The soap together with other emulsifying agents, phospholipid (present in the pancreatic juice and the bile) and the bile salts, rapidly break up the masses of fat into minute particles, greatly increasing the surface presented to lipase action. Splitting proceeds rapidly and is speeded up by the prompt removal of the split products by absorption. In the absorption the bile salts are especially useful. The exact mode of action of these substances is not known, but several factors enter and are important. First, they form water soluble, diffusible compounds with the fatty acids. Second, they are excellent wetting agents and penetrate easily into the complicated absorbing surface. They have an affinity both for fatty acids and the watery absorbing surfaces and in this way carry the water insoluble fatty acids into close contact with and eventually through the walls of the epithelial cells. The water soluble form necessary for the absorption of the fatty acids is thus provided by the bile salt combination. Another water soluble form of the fatty acid is its sodium salt called soap. The importance of soaps in fat absorption has been a matter of dispute for many years and is now recognized as secondary. The reaction of the intestinal contents is generally slightly on the acid side of neutrality and, under these circumstances, soap if formed would soon be broken up again. Also it has been found that soap in any considerable concentration is irritating and destructive to the intestine. It is apparently useful in the first stages of fat metabolism, emulsion formation and hydrolysis, after which the bile salts become the major agent in absorption.

During its stay in the epithelial cells the absorbed fatty acid is recombined into fat before being passed out of the cells into the collecting system, which in the case of the fats is the lymph. A number of factors

appear to be involved in this resynthesis. Sinclair²³ showed by the use of fats of pronounced characteristics, coconut and cod liver oils, that the phospholipids of the epithelium were involved, since the newly absorbed fatty acids were found in the epithelial phospholipid in amounts sufficient to indicate that most or all of the absorbed fatty acids passed into the framework of the intestinal phospholipids. These therefore constitute a stage in the absorption process. The resynthesized fat appearing in the thoracic duct is generally not the same as the absorbed fat but differs from it in degree of unsaturation, melting point and mean molecular weight of the fatty acids. These differences seem to mean either that the degree of unsaturation is adjusted (up or down) in the epithelium or that there is a mixing of the absorbed fat with fat brought from nearby depots. There appears to be an attempt to adjust the melting point of the incoming fat to a point near to body temperature, since high melting fat when fed appears in the chyle with a considerably lower melting point, and low melting fat has its melting point adjusted upward.²⁴ That there is a dilution of absorbed fat with body fat appears probable from recent work.²⁵ As to the fate of the absorbed fat, the belief has always been that it passes into the lymph system and enters the blood stream as fat via the thoracic duct. All efforts to demonstrate other paths of absorption, e. g. the blood stream via the portal system, have so far been unsuccessful. On the other hand, it has never been demonstrated that all the absorbed fat passes into the blood by way of the thoracic duct; in fact, recent attempts to recover absorbed fat from the thoracic duct have given remarkably small returns.²⁶ As noted earlier in the discussion, fat is believed to be hydrolyzed and then absorbed as fatty acid and glycerol, but the possibility of absorption in the unhydrolyzed state has never been entirely eliminated. Furthermore, the manner of passage of the resynthesized fat out of the epithelial cells and into the lacteals of the villi is not known nor is the method of

23. Sinclair, R. G.: The Role of the Phospholipids of the Intestinal Mucosa in Fat Absorption, with Additional Data on the Phospholipids of the Liver and Smooth and Skeletal Muscle, *J. Biol. Chem.* **82**: 117 (April) 1929.

24. Bloor, W. R.: On Fat Absorption: III. Changes in Fat During Absorption, *J. Biol. Chem.* **10**: 517, 1913-1914.

25. Little, J. M., and Robinson, C. S.: The Transportation of Absorbed Lipids, *Am. J. Physiol.* **134**: 773 (Nov.) 1941.

passage out of the blood into the storage and tissue cells any better understood. The best explanation of the latter two processes, and of the absorption of unsplit fat if any is absorbed, is that the fat passes the cell membrane by solution in it, as in the case of water soluble molecules, the phospholipid of the membrane aiding in the process.

Frazer^{25a} and associates have reopened the subject of fat absorption and have presented experimental evidence to indicate that fat may be absorbed without hydrolysis and indeed that such absorption may be an important procedure in the normal animal.

A considerable portion of the absorbed fat appears promptly in the liver, which is for fat, as it is for other foods, a place of temporary storage for excess food which would otherwise flood the organism and probably be wasted either by unnecessary combustion or by excretion. Of the fat thus mobilized to the liver a considerable portion, perhaps all of it, is changed to phospholipid and then probably a large percentage is discharged into the blood and distributed to other tissues. The change of fat to phospholipid in the liver appears to be a necessary step for its later use. If formation of phospholipid is prevented there is an accumulation of fat, which in extreme instances may amount to half the liver weight and which eventually leads to death as the result of interference with normal liver function. The main cause of the fat accumulation has been shown to be a lack of the base choline, a necessary constituent of lecithin, since the fatty liver may be prevented and cured by the administration of choline. When choline or its "makings" are lacking, lecithin cannot be formed and the fat accumulates. The story is not quite as simple as that because of the involvement of other factors. For example, there is always some cholesterol ester present in the accumulated fat, and the amount is larger when there is much cholesterol in the diet. The formation of cholesterol esters with the fatty acids and their storage appears to be one of the means used by the organism for disposing of excess cholesterol as well as excess of certain fatty acids, especially the more highly unsaturated ones.²⁶ The accumulation of cholesterol esters is always

25a. Frazer, A. C.: Fat Absorption and Its Relationship to Fat Metabolism, *Physiol. Rev.* 20: 561, 1940.

26. Kelsey and Longenecker.²⁶ Bloor.²⁶

more difficult to clear out of the liver than the fat. Instead of choline, substances which supply the material for making choline are effective in curing the fatty liver. Certain proteins, casein among them, are effective and the constituent of casein mainly responsible has been shown to be the amino acid methionine, of which the methyl group is the important part (there being three methyl groups in choline).

The fate of the phospholipid formed in the liver and hence the fate of the fat from which it was formed is not known. The use of tracer substances has not given clear answers, since their use has shown, along with pertinent facts, that constituents of living tissues are in a continuous state of flux. In the proteins, whole sections, single amino acids or parts of amino acids may be taken out and replaced by new ones without the chemical composition of the protein being appreciably changed.¹³ Similarly, in the case of the phospholipids, the phosphorus and the fatty acids have been shown to be replaceable by similar substances in the food. Probably choline and glycerin are also replaceable, so that the finding of a phospholipid in muscle which has the same labeled fatty acid or phosphorus which was found earlier in the liver need not mean that the liver phospholipid has been transferred to the muscle, although it may have been.

A second function of the liver in fatty acid metabolism which has been recently shown to be important and perhaps essential is its ability to break the long carbon chains of the fatty acids into four carbon fragments which appear sometimes as acetoacetic acid ($\text{CH}_3\text{CO}\cdot\text{CH}_2\text{COOH}$), sometimes as beta-hydroxybutyric acid ($\text{CH}_3\text{CHOH}\cdot\text{CH}_2\text{COOH}$) and sometimes as acetone (CH_3COCH_3). These substances, known as acetone bodies or ketone bodies, have been known for a long time but have been regarded as dangerous by-products in fatty acid metabolism, dangerous because they are fairly strong acids and use up significant amounts of the metallic bases of the body for their neutralization and excretion. They appear in the blood and urine of human beings and some other animals when a large proportion of the energy is supplied by fat, as in starvation or in untreated diabetes mellitus. They were considered to be the partially oxidized last four carbon atoms in the fatty acid chain,

which were what was left after successive β oxidation and which for some unexplained reason were unoxidizable unless carbohydrate was being burned at the same time ("fats can burn only in the fire of the carbohydrates"). Work in the last ten years (summarized by Stadie and his associates²⁷) has shown (a) that these substances are normally formed from fat in large amounts by the liver and to a considerable extent by the kidney, more than ten times the amount which appears in the urine, (b) that they are burned by muscle and other tissues, which however cannot form them, and (c) that they may supply most of the energy needed by the heart and presumably other tissues. The demonstration that these ketone acids can be formed and used by normal tissues in amounts large enough to account for the total amount of fat metabolized puts an entirely new face on their importance and use in the organism, raising them from the status of harmful and occasional accidents to that of regular stages in fatty acid breakdown.

In many ways these substances are analogous to lactic acid which appears in carbohydrate breakdown. They appear in excess in blood and urine whenever unusual pressure is put on the organism to burn fat, just as lactic acid appears in excessive amounts in blood, urine and sweat when unusual pressure is put on the carbohydrate burning mechanism, as in heavy muscular work. They are relatively strong acids, call for neutralization to about the same extent, and have the same or only slightly greater potential menace to the state of neutrality in the organism as lactic acid. In their formation from fatty acids there is considerable energy loss just as there is in the change from glycogen or *d*-glucose to lactic acid. The loss is probably much greater in the case of the ketone acids because it is due to oxidation while the diminished energy value of lactic acid is due to internal rearrangement in the breaking of the glucose molecule. The liberation of energy in the change from glycogen to lactic acid is put to good use in bringing about the recovery of the contraction mechanism of the muscle. No consideration has as yet been given to the much greater liberation of energy in the change from a C_{16} fatty acid to four 4 carbon ketone

27. Stadie, W. C.; Zapp, J. A., Jr., and Lukens, F. D. W.: The Effect of Insulin on the Ketone Metabolism of Normal and Diabetic Cats, *J. Biol. Chem.* **132**: 423 (Jan.) 1940.

acids, but there is little doubt that it could be and probably is put to similar uses. In the changes involved in the formation of lactic acid from glycogen or *d*-glucose, phosphoric acid figures largely. The participation of phosphoric acid in the metabolism of the fatty acids has not been demonstrated beyond the first stage, that of phospholipid formation from fat, but it seems probable that much if not all of the metabolized fat does go through the phospholipid stage. As has already been noted, not much is known about the fate of the phospholipid formed in the liver, but since the ketone body acids are also formed there the obvious next step would be the formation of ketone acids from the fatty acids of the phospholipid and, if the analogy with lactic acid holds, they are formed by way of intermediate phosphorylated compounds. Nothing has yet been done to elucidate these later stages of fatty acid metabolism.

NUTRITIONAL VALUE OF FATS

Very little need be said about the relative nutritional value of fats and hence of availability and distribution for the reason that most of the ordinary food fats of both plant and animal origin consist mainly of the same few fatty acids—oleic, palmitic and stearic—in varying proportions, and it is to be expected that they would not differ much in digestibility or in metabolic usefulness. This is found in general to be the fact.²⁸ When the melting point is high, digestion is slower and there is a tendency for unabsorbed fat to appear in the feces. The rate of absorption of various fats was found by one group of investigators²⁹ to be in the following order: linseed (best), then olive, whale, soybean, peanut, lard (rancid), cottonseed, cocoa butter, coconut and palm, but all were well utilized. Fats with a melting point above 37.8 C. were slowly absorbed. Laxative effects were noticed in only two fats of a series of sixty-three fats fed at a 50-115 Gm. level to human subjects. These were cocoa butter and goose fat.²⁸ At 140 Gm. a day, beef fat was laxative. Hydrogenated oils, as long as the melting point remains below 37.8° C., are as well absorbed as the natural oils,

28. Langworthy, C. F.: *The Digestibility of Fats*, J. Indust. & Engin. Chem. 15: 276 (March) 1923. Holmes, A. D.: *Digestibility of Fats Taken from Different Parts of the Animal Body*, J. Oil & Fat Ind. 3: 11 (Jan.) 1926.

29. Steenbock, Harry; Irwin, Margaret, H., and Weber, Janet: *The Comparative Rate of Absorption of Different Fats*, J. Nutrition 27: 103 (July) 1936.

Fats made up of the shorter chain fatty acids would have a lower caloric value than those containing the ordinary longer chains but the amount of these short chain glycerides in the ordinary diet is probably not large enough to influence nutritional calculations.

Natural fats carry in solution a number of non-fat substances some of which, for example, the fat soluble vitamins, are useful and desirable but have little importance in the metabolism of fat as such. Other fat soluble substances such as the sterols may in some cases be useful, as for example cholesterol in animal fats, while the sterols of plant fats are not useful because they are not absorbed by animals. This fact is made use of in treating certain individuals who have difficulty in excreting cholesterol, a shift from an animal to a plant diet stopping the cholesterol inflow.

Milk fat or butter contains, in addition to the common fatty acids, oleic, palmitic and stearic, considerable amounts of short chain fatty acids from butyric (C_4) up to C_8 which are presumably especially useful to the young animal. Milk fat contains also small amounts of cholesterol and phospholipid and varying amounts of the fat soluble vitamins or their mother substances. Egg fat is especially rich in phospholipid, cholesterol and vitamins. The fatty acids in both milk fat and egg fat are not especially notable since they originate largely from the food of the mother.

Aside from those well known dietary factors or vitamins which are essential for the general well-being of the living organism, two others have been found to be essential for the proper carrying on of fat metabolism. These are choline, the lack of which causes fatty livers and eventually death through liver failure, and certain "essential" fatty acids the nature of which is not entirely established. One, and perhaps the main one of these, is arachidonic acid, although linoleic and linolenic acids are effective in curing the fat deficiency disease.¹⁶ They appear to do so by transformation into arachidonic acid.

Since choline or its "makings" are essential for the necessary phospholipid stage in fat metabolism, materials for its synthesis must be supplied by the food. Choline itself is found in foods containing lecithin or sphingomyelin, such as brain, egg yolk, glandular products, meat, especially heart muscle and to a less extent in other animal foods. It may be synthesized by the

organism. In its construction the methyl groups appear to be the critical constituents and there are not many sources of these. The most important one is the amino acid methionine, methyl homocystein or α -amino- γ -methylthiol-n-butyric acid, which readily yields its methyl group in a variety of reactions in the animal body.³⁰ Methionine is supplied in food proteins, and of these casein has been found to be a satisfactory source. Undoubtedly other "good" proteins or mixtures of protein would provide an adequate supply of methionine.

The essential fatty acids, especially linoleic, are widely distributed in both plant and animal fats and are found also in combination in starches, so that their supply in adequate amounts needs no special consideration. These acids are low in amount or absent in certain tropical seed fats, as for example coconut oil, which are used in making oleomargarine, and this fact has been urged as an objection to the use of oleomargarine instead of butter. However, commercial oleomargarine generally contains a considerable proportion of animal fat, and most diets contain enough other sources of these acids to make up for any deficiency. On the other hand, marine animal fats contain large amounts of the essential fatty acids.

As sources of the essential fatty acids may be listed brain, organs and tissues of animals which are not deficient in these acids, and several natural fats generally with a high iodine number (degree of unsaturation) such as cod liver oil, corn and cotton oil, butter and egg yolk (provided the source animals are not fat deficient). Linseed oil is rich in the necessary acids but is unpalatable unless specially treated. In fact, most of the natural oils (liquid fats) will yield enough of the required essentials if taken in ordinary amounts.

30. du Vigneaud, Vincent; Cohn, Mildred; Chandler, J. P.; Schenck, J. R., and Simmonds, Sofia: The Utilization of the Methyl Group of Methionine in the Biological Synthesis of Choline and Creatine, *J. Biol. Chem.* **140**: 625 (Aug.) 1941.

CHAPTER IV

CALORIES IN MEDICAL PRACTICE

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Calories in medical practice are just as important as they ever were, in spite of the fact that attention has been centered on the vitamins. No supplements of vitamins or mineral elements can alter the laws of the conservation of energy. Calories are still needed to keep the body warm and to furnish energy for muscular work.

Calories, or British thermal units, form the basis of calculations in engineering, in the estimation of the heating values of commercial fuels and in the estimation of the feeding of populations. Perhaps in the latter connection they may determine the outcome of the present war. A physician, however, is directly concerned with calories in relatively limited fields. He must know the calories of the basal metabolism, he must understand the construction of an adequate diet in both health and disease and he must know how to construct high or low calory diets that contain the essential food elements. Although he does not often realize it, he is intimately concerned not only in the administration of calories in the food but also in their dissipation through the surface of the body. It is the temporary disproportion between gain and loss that causes the ups and downs of fever.

The unit of heat measurement that concerns the physician is the large calory, the kilocalory, the amount of heat required to raise 1 Kg. of water 1 degree C. The small calory, the amount required to raise 1 Gm. of water 1 degree C., is a unit employed by physicists and chemists for the calculation of energy changes in intermediary metabolism and is so seldom mentioned by physicians that it is rarely found in medical literature. When employed clinically, it causes endless confusion. The British thermal unit is the heat required to raise 1 pound of water 1 degree F. and equals 252 small calories. Fortunately this term is not used in medical

literature. The amount of heat given off by the resting man of average size is about equal to the heat of a 60 watt electric bulb or the flame of an alcohol lamp about 1 inch high. A man exercising hard equals the heat of ten such lamps. Most of us fluctuate between these two extremes in the course of a day, and it is extremely difficult to make a really accurate estimate of the number of calories that a person consumes on any one day.

The basal metabolism or basal metabolic rate is a term generally employed to indicate the heat production of a person fourteen or more hours after the last intake of food at complete physical and mental rest in a comfortable environment. This is sometimes called the postabsorptive metabolism, or standard metabolism, theoretically better than basal metabolism because the lowest metabolism is found during sleep or inanition or after the removal of the thyroid gland. Basal metabolism is most conveniently measured early in the morning in the person who has come to the laboratory without breakfast with relatively little physical exertion. Persons in good health can travel for as much as an hour before the test and be in basal condition after resting for one-half to one hour. A person moderately ill with toxic diffuse goiter may be affected by an automobile ride of one-half hour. One who is seriously ill should have the test made in the same building in which he spends the night. The stimulating effect of food, the specific dynamic action, is slight ten hours after the last meal unless that meal has been a heavy one. Even a small breakfast has little effect after three or four hours. Much more serious than the 2 to 3 per cent increase from a small breakfast is an increase of 10, 20 or even 50 per cent which may be caused by fear, apprehension or discomfort shortly before or during the test. The most important precaution is prevention of such tension by means of preliminary tests, careful explanation on the part of the physician and a quiet atmosphere during the test. A high percentage of determinations in toxic diffuse goiter are ruined because the patient has been told by her friends or even by her physician that the results will decide whether or not she is to have an operation.

After the test has been made the physician should always try to form an estimate of the emotions during

the whole procedure. He should note carefully the pulse rate before and during the test and compare it with the rate obtained while the patient was in bed on other days. A significant rise in pulse rate usually indicates an unreliable determination. The physician should also question the patient regarding apprehension and discomfort. An experienced patient may tell you "The test I had in Dr. Blank's office was about 20 per cent too high."

First tests on inexperienced patients or normal controls are usually 5 to 10 per cent higher than subsequent tests. Most of the older standards of metabolism were based largely on first tests and are therefore 5 to 10 per cent too high when applied to the more modern series of controls founded on results obtained with experienced subjects. It may therefore be said that normal and trained healthy subjects average 5 to 8 per cent below the so-called Aub-Du Bois standards of 1917, or the Mayo Clinic Boothby, Berkson and Dunn standards of 1936, or about 3 per cent lower than the Harris-Benedict standards. The Aub-Du Bois standards were much too high for children, and the Bierring figures for the boys and the Kestner-Knippling tables for girls are more accurate for well trained children.¹ Some day there will be more satisfactory physiologic standards, but even after the thousands of determinations that have been made on normal subjects it is too soon to settle on a new level, since the average normal is still falling slightly every decade. Some recent work by Hardy and Milhorat² showing the effect of temperature in changing the metabolism of women but not of men was disturbing. On the average the metabolism of women is 10 to 12 per cent lower than that of men of the same size, but in a cold environment it may be the same as that of men and in a very warm environment may be 15 to 20 per cent lower. In spite of all these limitations clinicians get along quite well with the old standards to which they are accustomed, estimating, that for well trained subjects and good satisfactory tests most normal persons come within + 5 to - 20 per cent of the so-called standard. Some few normal persons are

1. Webster, Bruce; Harrington, Helen, and Wright, L. M.: *J. Pediat.* 19: 347 (Sept.) 1941.

2. Hardy, J. D.; Milhorat, A. T., and Du Bois, E. F.: *J. Nutrition* 21: 383 (April) 1941.

5 per cent further off in either direction. Boothby, Berkson and Dunn³ have emphasized the fact that a person toward the limits of the normal range may be normal but that the chances are greatly against it. Conversely, some exceptional persons with pathologically low or high metabolism may come within the normal range. The basal metabolism by itself should be considered merely as one piece of evidence and never the final answer. One book on metabolism ends with this sentence: "God forbid that we make our diagnoses by machinery."

It must be admitted that the basal metabolism tests are seldom of great value except in the diagnosis and treatment of diseases of the thyroid gland. The vast majority of basal metabolism tests, like the vast majority of roentgenograms, show normal conditions. Tests are necessary to avoid missing cases which present suggestive histories but which do not show the usual clinical signs. Basal metabolism tests and other laboratory tests are probably overdone, but it is doubtful whether this can be remedied.

There are obviously many factors which influence the total heat production apart from those of size, age and sex that are used in calculating the basal metabolic rate. Some of the more important factors are shown graphically in figure 1. This illustrates not only heat production but also heat loss and shows how one influences the other. Ordinarily, any increase in heat loss is met by an increase in heat production, and vice versa, with a balance so delicate that the body temperature is maintained with extraordinary uniformity. In health it is only on occasions when heat production is greatly and suddenly increased that heat loss lags behind, causing a rise in body temperature. Nevertheless, a short bout of hard exercise can raise the rectal temperature to 38 to 39 C. (100.4 to 102.2 F.) for half an hour. Conversely, a sudden change to a cold environment without compensating exercise can cause a drop in temperature.

Basal heat production may have superimposed on it the specific dynamic action of food. After a heavy meal of protein or carbohydrate, or both, there is a gradual increase in metabolism, perhaps rising 30 to 40 per cent above the basal rate in two or three hours and then

3. Boothby, W. M.; Berkson, J., and Dunn, H. L.: *Am. J. Physiol.* 119: 468 (July) 1936.

falling slowly. After ordinary meals the rise is less noticeable but when distributed throughout the twenty-four hours under ordinary conditions the total specific dynamic action amounts to about 6 per cent of the total caloric value of the food. This is small in comparison with the large increase that might be caused by certain diseases such as hyperthyroidism with figures of 15 to 100 per cent or more above the basal rate. The unconscious tensing of the muscles that accompanies appre-

FACTORS INCREASING

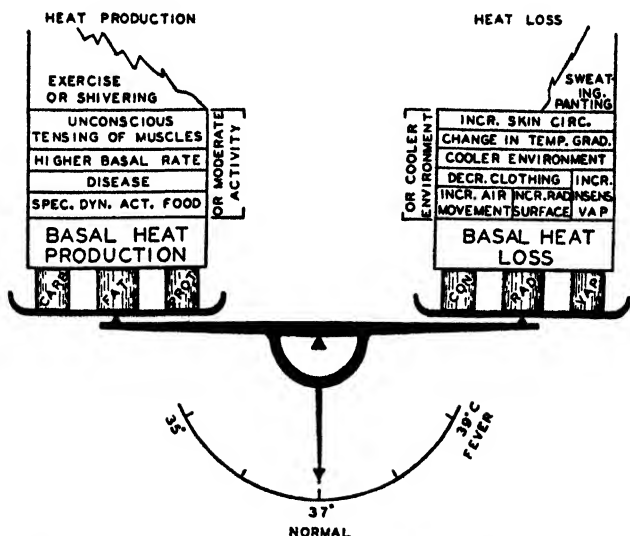


Fig. 1.—Balance between the factors increasing heat production and heat loss.

hension may raise the heat production 10 to 20 per cent without its being noticed by an inexperienced observer. Moderate activity causes a rise of 20 to 50 per cent, whereas hard exercise may increase the metabolism three or four or even ten fold. When there is fever there is an elevation of about 13 per cent for each degree centigrade, but the variations are considerable.

Heat loss may be an important element in raising heat production. If a man goes into a cooler environment or is exposed to a strong wind or takes off some of his

clothing, or even stretches so that he exposes a larger surface, he loses more heat and in order to compensate the body has to produce more calories. As a rule, a person does this by voluntary exercise or involuntary shivering. Conversely, if the man has produced an unusual amount of heat by exercise he tries to disseminate it by seeking a cooler environment or by taking off some of his clothing. If this is not sufficient he breaks into a sweat, which cools the skin through vaporization. Dogs and other animals without sweat glands lose excess heat by panting.

The mechanism of heat loss is of interest to the medical man, since it forms the basis of air conditioning. When a person is quiet in a moderately cool room most of the heat is lost through radiation from the warm surface of the body and warm clothing to the cooler walls and especially to the windows. The body gains heat through radiation from the heating apparatus and from lamps. Under ordinary conditions about 25 per cent of the calories are lost through the vaporization of water from the skin and lungs, but with the outbreak of even small amounts of sweat this percentage rises. When the air and surrounding objects are warmer than the surface of the skin vaporization becomes the sole channel of heat loss. The percentage of calories lost by convection through the movement of air is extremely variable. In a quiet room a very quiet person may lose only 12 to 15 per cent of his heat in this manner, but the percentage rises roughly according to the square root of the velocity of the air movement. Even small motions of the body cause a considerable increase in the flapping effect of clothing.

The human body in a cold environment is able to conserve its calories by changing the skin and subcutaneous tissue into a suit of clothing. The peripheral blood flow is reduced almost to zero and the skin becomes as good an insulator as an equal thickness of leather or cork. When the body needs to lose heat the peripheral blood flow is increased and the warm blood from the interior of the body comes in contact with the skin, which is cooled by the vaporization of sweat. The most effective sweating leaves no visible water on the surface; sweat that drips is wasted, since it removes no heat. In this loss of heat the hands and feet are relatively unimportant, since they constitute

only a small percentage of the total surface. Circulation in the hands is not necessarily a good indicator of the average circulation or of the total heat loss because the hands respond to emotion more than any other part of the body. The feet and especially the toes are not good indicators of the average condition of the skin because they are far from the source of heat and have large radiating surfaces. In cold weather the skin of the toes may show temperature readings below that of the dry bulb thermometer. The toes resemble wet bulb thermometers.

In one of the older hospitals in New York there was a women's ward on the north side of the building that was difficult to heat on a cold winter night. In making rounds after such a cold night it would be noted that most of the patients showed a subnormal temperature and that many of the older women had temperatures alarmingly depressed. Here was a combination of low heat production on the part of the old women and high loss through radiation and convection. Their feet were icy cold, and since many of them had impaired peripheral circulation the situation was serious. At the present time in Russia when the weather is so extremely cold, if a soldier who has been keeping up his heat production by marching or fighting is wounded and has to remain quiet the heat loss will exceed heat production to such an extent that there will be a decided fall in body temperature contributing to the rapid production of shock. The same thing, to a lesser extent, can happen in our own climate when a man is injured outdoors. It can happen even in the accident ward of a hospital. Going to the other extreme, a man in shock might be surrounded by so many hot water bottles and blankets that in the effort to lose calories a large amount of blood needed internally is diverted to the skin and a large amount of water and salt lost through dripping sweat.

In health the normal temperature of the body is regulated delicately at about 36.9 C., a little lower in the early morning, higher in the late afternoon. Minor or even moderately large changes in heat production or heat loss are balanced, as shown in the diagram (fig. 1). In fever the temperature regulating center in the hypothalamus seems to be adjusted at a different level, sometimes fairly constant, usually fluctuating 2 to

3 degrees C. during the day. When the temperature regulating center is suddenly set at 40 C., the body at the normal temperature of 37 C. (98.6 F.) finds itself 3 degrees too cool and therefore calls into play the mechanism of increased heat production, sometimes supplemented by the skin mechanism which diminishes heat loss. If the change in the temperature regulating center is sudden, as in malaria, the body has to warm itself by means of shivering. In most fevers the change can be made more gradually. If the patient has attained a high temperature, say 40 C., and the heat regulating center is suddenly adjusted to the normal of 37 C., the body finds itself 3 degrees too warm, calls into play the mechanism of heat loss and loses calories rapidly through sweating.

In diseases of high metabolism, for example toxic diffuse goiter, the body is faced with the continuous problem of losing abnormally large amounts of heat. Therefore, the peripheral circulation is greatly increased and sweating may be necessary even in moderately cool atmospheres. The patient cannot tolerate as much clothing or as many blankets as the normal person. At the other extreme, persons with low metabolism, as in myxedema or inanition or old age, are obliged to restrict the loss of heat by diminishing the peripheral blood flow. They need warm clothing, especially since they are unable to keep themselves warm by exercise. These illustrations emphasize the importance of balance of calories. The physician is responsible not only for putting them into the patient but also for seeing that they are conserved or eliminated in the proper manner. Heat loss is just as important as heat production.

There are certain diseases in which not only the basal metabolism but also the total metabolism is decidedly raised. Chief among these comes toxic diffuse goiter, with an increase in the basal metabolism which may be 75 per cent or more. In addition, the restlessness of the patient and the muscular inefficiency in performing tasks raise the total requirement far beyond the basal rate. Emotional storms constitute an added caloric burden. There is also an increased metabolic rate in many patients with lymphatic leukemia, pernicious anemia, some patients with acromegaly, some with heart disease, and nephritis, particularly if the patient is dyspneic. There is a rise in metabolism in fever,

perhaps as much as 40 per cent in a patient with a temperature of 40 C. (104 F.). If the patient is restless or delirious or coughing, the total metabolism is affected more than the basal. Agitated mental patients may have a very high requirement.

The depression of the basal metabolism in so-called complete myxedema is usually around 35 to 40 per cent. A similar decrease may be found with extreme inanition. Elderly patients who lie quietly in bed have surprisingly low total metabolisms.

There may be considerable loss of ingested calories in the feces, as for example in pancreatic or hepatic disease with poor absorption of fat. Interference with bile flow or with the abdominal lymph channels may also affect fat absorption.⁴ Excretion of fat may be extremely important in the feeding of premature infants.⁵ Of the 120 calories per kilogram of body weight contained in the daily diet, 10 to 30 per cent may be lost as fat in the feces. The loss is reduced by lowering the fat intake. Full term infants usually waste less than 10 per cent of the food calories by fat excretion. Roughage or indigestible carbohydrate residue increases the fecal excretion of nitrogen, presumably from endogenous secretions. Recent interest in whole wheat cereals has led to a confirmation of the loss of nitrogen but has shown no interference in the digestion of fat or carbohydrate.⁶ These observations on men should be extended to children and patients who may be less able to tolerate roughage. In diabetes the caloric loss from glycosuria, which may be considerable, should be subtracted from the available calories of the food. Fortunately, with insulin extremely great losses are now rare.

The caloric needs of children form a chapter in themselves and the criteria are different from those of adults. Extra food must be given to take care of growth; large proportions of calories are needed to meet the incessant activities of playing children and athletic young men. In general, the food allowance for a child over 12 years should be about the same as that of an average adult, or more than 2,500 calories a day. An active boy of 15 or 16 years may use 4,000 calories a day.

4. Verzar, F., and McDougall, E. J.: *Absorption from the Intestine*, New York, Longmans, Green & Co., 1936.

5. Gordon, H. H., and McNamara, Helen: *Fat Excretion of Premature Infants*, *Am. J. Dis. Child.* 62: 328 (Aug.) 1941.

6. Sealock, R. R.; Basinski, D. H., and Murlin, J. R.: *J. Nutrition* 22: 589 (Dec.) 1941.

Bearing all these factors in mind, it is usually possible to form a rough estimate of the calories produced by a normal person or a person with a given disease. Since the basal metabolism of different persons may vary 10 to 15 per cent from the average and since in the same person it may vary 5 to 15 per cent from day to day, it is obvious that one cannot make an accurate prediction. Moreover, the basal metabolism is only a small proportion of the total metabolism unless the person is confined to strict bed rest. Therefore, in estimating the total caloric requirement it is almost impossible to guess the basal metabolic requirement within 100 to 200

TABLE 1.—*Total Energy Requirement Every Twenty-Four Hours, Including Eight Hours of Labor, as Estimated by Becker and Hämäläinen*

Men	Calories
Tailor.....	2,000 - 2,800
Bookbinders.....	3,000
Shoemakers.....	3,100
Metal workers.....	3,400 - 3,500
Painters.....	3,500 - 3,600
Cabinet makers.....	3,500 - 3,600
Stone masons.....	4,700 - 5,200
Wood sawers.....	5,500 - 6,000
Women	
Seamstress (with hand needle).....	2,000
Seamstress (with machine).....	2,100 - 2,300
Bookbinder.....	2,100 - 2,300
Household servants.....	2,500 - 3,200
Washerwomen.....	2,900 - 3,700

calories. Still, in figuring out a dietary it is a help to estimate the person's height and weight, find the age and figure out the basal metabolism without bothering to calculate closer than the nearest 100 calories. For a person quiet in bed one can add 10 per cent; a patient moderately active, 30 per cent; a patient out of bed in the sickroom during the day but moderately quiet, 50 per cent. The day may be divided into hours of sleep, rest, moderate activity and the like; then one can estimate the calories consumed each hour and add the total of estimates. Fortunately, it is seldom necessary to come within 200 to 400 calories of the total metabolism. One of the best checks, nature's own, is the appetite, which in most normal persons regulates the weight with surprising accuracy. This regulation varies in disease and is notoriously faulty in the obese.

Fairly accurate measurements are made in metabolism wards in which some patients are in bed and others are carrying on a moderate amount of activity. All the food eaten by each patient is carefully weighed and the excreta are collected and analyzed. Changes in body weight are charted daily and the food intake is adjusted to maintain an approximately uniform body weight. In laboratories equipped with a large respiration chamber or calorimeter in which a man may remain for several days, measurements of total metabolism can be made within 5 per cent. This can be balanced against the food intake, but the normal activity of the person is somewhat restricted. For the person who is outdoors

TABLE 2.—*Recommended Daily Allowances for Calories (Food and Nutrition Board, National Research Council)*

	Calories per Day	
70 Kg. man, fairly active.....	3,000	
very active.....	4,500	
sedentary.....	2,500	
56 Kg. woman, fairly active.....	2,500	
very active.....	3,000	
sedentary.....	2,100	
Children		
Under 1 year..	100/Kg.	
1 - 3 years.....	1,200	
4 - 6 years.....	1,600	
7 - 9 years.....	2,000	
10 - 12 years.....	2,500	
13 - 15 years.....	2,800 girls	3,200 boys
16 - 20 years.....	2,400 girls	3,800 boys

working, the total requirement can be estimated from the tables of occupations given in the textbooks of physiology and dietetics, for example, table 1.⁷ The Food and Nutrition Board of the National Research Council⁸ recently has recommended the general standards of caloric requirement for children and adults under average conditions given in table 2. A good deal depends on temperament and habit, since there may be two clerks in the same office, one slow moving and placid and the other quick and nervous, who will have quite different requirements. One man takes the elevator or walks up stairs slowly, the other runs up stairs. Walking at a rate of 5 miles an hour requires about 50 per cent more energy than walking at 3 miles an hour.

7. McLester, J. S.: *Nutrition and Diet in Health and Disease*, ed. 3, Philadelphia, W. B. Saunders Company, 1940, p. 65.

8. Recommended Allowances for the Various Dietary Essentials, current comment, *J. Am. Diet. A.* 17: 565 (June-July) 1941.

The calculation of the calories produced is only the first step in estimating the calories of the diet. The physician may wish to give more calories than the "requirement" to a person who is thin or who is convalescent from an acute disease. On the other hand, he may wish to give an amount of food below the total expenditure in order to reduce weight or to diminish the metabolism or the total work of the circulation. Again he may desire to give an amount equal to the expenditure but may be limited by the lack of appetite or the condition of the gastrointestinal tract. In a hospital ward there are relatively few patients whose heat production is even approximately equal to the number of calories they take in the food. Those acutely ill are living partly off the restricted diet and partly off their own body supply of fat and protein. Those who are convalescent are storing much of their food intake as body protein or body fat. In patients who are seriously ill the changes in weight are only partially due to changes in body protein and fat, since most of the fluctuations are caused by gain or loss in body water. Newburgh and Johnston⁹ have shown that this often occurs in the obese and that the patient, for a week or more, may lose large amounts of body tissue before there is a drop in weight. In the long run, provided there is no edema, the body weight is the best indication of the adequacy of a diet. The scale should be used regularly with the ambulatory patient, and frequent weighings are extremely valuable in those who are confined to bed (fig. 2).

Can a general basic diet be recommended which will fit the needs of the average patient in the hospital? Other requirements besides the caloric intake need to be considered. When the physician is confronted with a patient who cannot take a sufficient number of calories even with expert cooking and skilful nursing, he has the responsibility of seeing that the food administered contains the essential vitamins and minerals. If necessary, they can be supplemented by additional vitamins in concentrated form. In some hospitals this problem is met by recommending a general diet of 2,000 calories, containing 75 Gm. of protein, 100 Gm. of fat and 200 Gm. of carbohydrate. This general diet of 2,000

9. Newburgh, L. H., and Johnston, M. W.: *Ann. Int. Med.* 8:815 (Feb.) 1930.

calories seems to be an adequate standard for the average hospital patient, although its interpretation for each individual must be a liberal one. A supply of vitamins and minerals adequate for a normal person is provided by including in the diet the following "protective" foods: 1 pint of milk, 1 egg, 1 serving (3 to 4 ounces) of meat, 3 teaspoons (15 Gm.) of butter, 4 servings of whole grain bread or cereal, 2 vegetables other than potato 1 of which is raw, and 2 fruits 1 of

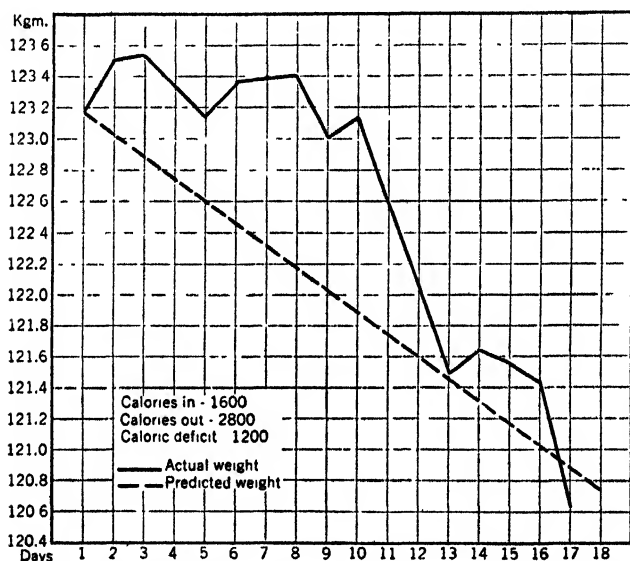


Fig. 2.—Weight loss curve. An obese subject first maintains her weight and then loses weight so rapidly that the total loss corresponds with the prediction. (Newburgh and Johnston.⁹)

which is raw. The "protective" foods thus supply about 1,200 of the 2,000 calories.

An appetizing menu may lead to a wide variation in the daily caloric intake. In one hospital¹⁰ a week's survey of the general diets as served showed a daily variation between 1,900 and 3,200 calories with an average of 2,570 calories. But the food served does not necessarily represent the food intake of the patients. When the patients in semiprivate rooms selected food

10. Unpublished data from the Department of Nutrition, New York Hospital.

from a menu of approximately 3,000 calories, about 25 per cent of the bread, butter and vegetables and 37 per cent of the salads were not eaten. The ward patients on a nonselective diet of 3,000 calories left between 5 and 10 per cent of the food served. When special diets are needed it is essential to know the food intake as well as the food prescription.

To meet special needs additional calories can be added to the general diet, such as an extra pint of milk during the latter part of the period of pregnancy. The extra energy required for lactation depends on the amount of milk produced. The extra food calories should be about twice those secreted in the milk, or approximately 700 to 1,500 calories of food for 500 to 1,000 cc. of milk. Dairy products are the preferred foods for supplying the extra calories. Excess caloric intake leading to fat deposition in the mother during the latter period of pregnancy influences lactation rather than the weight of the child at birth.¹¹

The energy requirements of the body under various conditions are calculated from the basal metabolism plus activity, as previously noted, according to the oxygen consumption and the physiologic combustion values of protein, fat and carbohydrate derived from Rubner's work. Since the foodstuffs vary in composition and degree of assimilation, the slightly lower values of Atwater are generally used for the calculation of diets in this country. Atwater's figures are 4 calories per gram for protein and carbohydrate and 8.9 calories for fat, although 9 for fat is frequently used. A recent review¹² has emphasized the lack of uniformity in specifying diet standards. For example, 100 Gm. of protein, 80 of fat and 500 of carbohydrate would represent 3,423 calories as purchased (allowing 10 per cent for kitchen and table waste), or 3,204 Rubner calories, or 3,112 Atwater net calories. The difference becomes significant when the results of laboratory experiments are translated to large groups of persons.

To simplify the calculation of diets, it has been a common practice to divide the vegetables and fruits into general classes according to their total carbohydrate content. Recent analyses by improved methods indicate

11. Garry, R. C., and Steven, D.: *Nutrition Abstr. & Rev.* 5: 855 (April) 1936.

12. Morey, N. B.: *Nutrition Abstr. & Rev.* 6: 1 (July) 1936.

that a reclassification of some of the foods is in order. The later figures for available carbohydrate tend to be lower than those in the generally accepted tables.¹³ Another possible error has appeared in the sample to sample variation of cooked vegetables. The discrepancy between the calculated carbohydrate calories and those determined by direct analyses was particularly large in boiled squash, parsnips and sweet potatoes.¹⁴

What is the optimum proportion of fat to carbohydrate in the diet from the standpoint of meeting the caloric needs of the body under various conditions? Exact data on this point are scarce. Economic factors dictate the diets of large parts of the population and thus lead to a relatively high percentage of the cheaper carbohydrates. This situation influenced the older standards such as Voit's, which called for 60 to 70 per cent of the calories in the form of carbohydrate. The recent emphasis on vitamin and mineral requirements and on the biologic value of proteins tends to increase the fats and decrease the carbohydrates. This is seen especially in the quoted 2,000 calory general diet for patients. Fat provides 45 per cent and carbohydrate 40 per cent of the calories, which together with 15 per cent from protein yield a respiratory quotient of 0.83. It is perhaps significant that a similar proportion of fat to carbohydrate (1:2 by weight) is found in human milk. When a free choice of food is possible, men doing heavy sustained work and athletes in training with high caloric intakes of 4,500 to 7,500 calories select a diet containing 15 per cent or more of the calories in protein and the balance about evenly distributed between fat and carbohydrate.¹⁵ Many of the observed respiratory quotients approach the median level of 0.85 in continued heavy exercise. If future research supports the present indication, a more abundant consumption of fat would be desirable for optimum nutrition.¹⁶

13. Williams, R. D.; Wicks, L.; Bierman, H. R., and Olmsted, W. H.: *J. Nutrition* **10**: 593 (June) 1940.

14. Carpenter, T. M.: *J. Nutrition* **10**: 415 (May) 1940.

15. Cuthbertson, D. P.: *Nutrition Abstr. & Rev.* **10**: 1 (July) 1940.

16. Anderson, W. E., and Williams, H. H.: *Physiol. Rev.* **17**: 335 (July) 1937.

CHAPTER V

WATER AND SALT REQUIREMENTS IN HEALTH AND DISEASE

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Salts and water of the body are inextricably bound in their interchange between organism and environment. This generalization applies particularly to sodium, potassium, chloride, bicarbonate, phosphate and protein, electrolytes which are the principal contributors to the pattern of intracellular and extracellular fluid. The exchange of these electrolytes and the exchange of water comprise the theme of this chapter. Several other electrolytes present in the human organism such as magnesium, calcium, lactate, iron, iodide and urate are osmotically unimportant for fluid balance and will not be discussed. The anatomy of body fluids, i. e. the structural compartments and the concentration of electrolytes, will be outlined first. It will be followed by an inquiry into the mechanism of the ingress of the several components into the body. The remainder of the review, which is proportionately longest, will be concerned with their egress from the body.

It is deemed most appropriate in the introduction to give credit to the masters in the field, Dill, Gamble, Hastings, Henderson, Peters, Smith and Van Slyke and others who by their researches, physiologic and clinical, have contributed in large measure to our present knowledge of body fluids. Several of their contributions have been freely drawn on in the preparation of this article.¹

THE ANATOMY OF BODY FLUIDS

The fluid structures of the body, as was Gaul, are divided into three parts, blood, interstitial fluid (including lymph) and intracellular fluid. The volume of interstitial fluid is the most labile of the three and

1. Dill, D. B.: *Life, Heat and Altitude: Physiological Effects of Hot Climates and Great Heights*, Cambridge, Harvard University Press, 1938. Gamble, J. L.: *Extracellular Fluid and Its Vicissitudes*, *Bull. Johns Hopkins Hosp.* **61**:151, 1937; *Renal Defense of Extracellular Fluid: Control of Acid-Base Excretion and the Ratio of Water Expenditure*, *ibid.* **61**:174, 1937. Peters, J. P.: *Body Water: The Exchange of Fluids in Man*, Baltimore, Charles C. Thomas, 1935. Henderson, L. J.: *Blood, a Study in General Physiology*, New Haven, Yale University Press, 1928. Smith,²

expands or contracts with the changing physiologic needs of the body such as occur during digestion, sleep or profuse sweating. In morbid disturbances of fluid balance this compartment likewise is the buffer between the other two and may undergo profound alteration that is not reflected in the volume of blood or volume of intracellular fluid. The resistance of these two compartments to change at the expense of interstitial fluid is an example of the rigorous and effective equilibrium exercised by the body, i. e. homeostasis. The concentration of electrolytes occupies an intermediary position with regard to capacity to change under varying stresses. The concentration of electrolytes is maintained within a narrow range in health in each of the three major compartments of body fluids. In sickness the concentrations of plasma and interstitial fluid electrolytes yield before the integrity of intracellular fluid is threatened.

The amount of fluid in the body is approximately 70 per cent of the total mass. This is distributed as follows: The volume of circulating blood plasma is approximately 5 per cent of the total body weight, or 3.5 liters in a person of 70 Kg. (154 pounds). Interstitial fluid comprises 15 per cent of body weight, or 10.5 liters. Intracellular fluid comprises 50 per cent of body weight, or 35 liters in a person of 70 Kg.

The values quoted have been derived from experimental procedures, direct and indirect. Plasma volume may be determined in the intact animal or in man by noting the dilution of an intravenously injected nontoxic dye by a method similar to that described by Gregerson, Gibson and Stead.² Only small amounts of plasma are needed for the determination if the readings are made in a photocolorimeter.³ Whole blood volume is calculated directly from plasma volume by taking into account the hematocrit reading. Interstitial fluid volume may be determined simultaneously if a few decigrams of sodium thiocyanate⁴ is injected with the dye. No satisfactory

2. Gregerson, M. I.; Gibson, J. J., and Stead, E. A.: Plasma Volume Determination with Dyes: Errors in Colorimetry; the Use of the Blue Dye T-1834, *Am. J. Physiol.* **113**: 54, 1935.

3. Gibson, J. G., 2d., and Evelyn, K. A.: Clinical Studies of the Blood Volume: IV. Adaptation of the Method to the Photoelectric Microcolorimeter, *J. Clin. Investigation* **17**: 153, 1938.

4. Crandall, L. A., Jr., and Anderson, M. X.: Estimation of the State of Hydration of the Body by the Amount of Water Available for Solution of Sodium Thiocyanate, *Am. J. Digest. Dis. & Nutrition* **1**: 176, 1934.

method has been devised for determining volume of intracellular fluid or of total body water in human beings. This is a serious void in the armamentarium of the clinical investigator. The values given for these components have been deduced from sacrifice experiments on animals.

The concentration of electrolytes in the fluid compartments of the body except blood is less amenable to experimental determination than are the volumes. Whole blood and plasma are the only phases that may be approached directly. The concentrations in interstitial fluid, however, are similar to their concentrations in a protein free filtrate of plasma. This is fortuitous and, if information is available concerning plasma,

Concentration of Electrolytes in Arterial Plasma

Bases		Acids	
	mEq. per Liter		mEq. per Liter
Sodium.. . . .	140	Chloride.....	104
Potassium . . .	4	Bicarbonate.. . . .	25
Calcium.... .	5	Protein..... .	17
Magnesium. . . .	2	Phosphate... . .	2
		Lactate...	1
		Undetermined.....	2
Total..... .	151	Total..... .	151

deductions concerning interstitial fluid are probably valid. The concentration of electrolytes in arterial plasma of a normal person is given in the accompanying table.

The concentrations in venous plasma, except for bicarbonate, are essentially the same as for arterial plasma. Inspection of the data shows that the sum of the acids equals the sum of the bases. The solution is slightly alkaline, the p_{H_s} ,⁵ which is an index of the hydrogen ion concentration, being 7.40. Within the limits p_H 4 to p_H 10 the contribution of H and OH ions to the foregoing summation would be negligible. The sum of the four bases may be expressed as total fixed base or total inorganic base. There is only a

5. The subscript s stands for serum. Practically, there is no difference between hydrogen ion concentration of serum and plasma. Since most of the experimental work is done on plasma rather than serum, a more appropriate designation would be p_{wp} in place of p_{ws} .

negligible quantity of organic base in the plasma of normal persons. Total fixed base may be determined with a high degree of accuracy by electrodialysis using not more than 0.2 cc. of material.⁶ If the bases are determined individually, 1 or 2 cc. of material is needed for the respective constituents (sodium,⁷ potassium,⁸ calcium,⁹ magnesium¹⁰). The value for the sum of the individual bases is useful as a check against total fixed base, while both are useful as a check against the sum of the determined acids. No single procedure has been devised for the determination of total acids as has been devised for total base. Organic and inorganic acids are present in health and in disease. The acids may be determined individually on 1 cc. or less of plasma (chloride,¹¹ bicarbonate,¹² proteinate,¹³ phosphate,¹⁴ lactate¹⁵). If microprocedures are employed it is possible to collect thoroughly reliable data of the complete acid-base pattern of plasma with not more than a total of 10 cc. of material, which may be obtained from 20 cc. of whole blood.

The nomenclature milliequivalents per liter (mEq./L) used to express concentration of constituents seems formidable to many physicians. It is no more mysterious, however, than milligrams or centimeters to the uninitiated. If concentrations are expressed in milliequivalents per liter, values for different constituents readily may be compared, as in the statement previously made that

6. Consolazio, W. V., and Talbott, J. H.: The Determination of Total Base in Biological Material by Electrodialysis, *J. Biol. Chem.* **132**: 753, 1940.

7. Butler, A. M., and Tuthill, E.: An Application of the Uranyl Zinc Acetate Method for Determination of Sodium in Biological Material, *J. Biol. Chem.* **93**: 171, 1931.

8. Consolazio, W. V., and Talbott, J. H.: Modification of the Method of Shohl and Bennett for the Determination of Potassium in Serum and Urine, *J. Biol. Chem.* **126**: 55, 1938.

9. Clark, E. P., and Collip, J. B.: Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, *J. Biol. Chem.* **63**: 461, 1925.

10. Cruess-Callaghan, G.: A Method for the Microdetermination of Magnesium, *Biochem. J.* **29**: 1081, 1935.

11. Keys, A.: Microdetermination of Chlorides in Biological Materials: Presentation of Method and Analysis of Its Use, *J. Biol. Chem.* **119**: 389, 1937.

12. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, *J. Biol. Chem.* **61**: 523, 1924.

13. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company **2**: 516, 1932.

14. Tschopp, E., and Tschopp, E.: Ueber die Reduktion der Phosphormolybdänsäure zu "Molybdänblau" und über die quantitative Bestimmung von Phosphat- neben Silikat- und Arsenationen in der Biologie, *Helvet. clin. acta* **15**: 793, 1932.

15. Edwards, H. T.: Simplified Estimation of Lactate in Normal Human Blood, *J. Biol. Chem.* **125**: 571, 1938.

the sum of the bases should equal the sum of the acids. Comparison would be impossible if a heterogeneous nomenclature were used and sodium were expressed as milligrams per hundred cubic centimeters, protein as grams per hundred cubic centimeters and bicarbonate as volumes per hundred cubic centimeters.¹⁶

Sodium and chloride comprise the bulk of the electrolytes in plasma and interstitial fluid. The presence of potassium in plasma is little more than evidence of its migration to and from intracellular spaces. Protein is essential for maintenance of osmotic pressure in the blood. It is expressed as the acid proteinate in the table. Bicarbonate and phosphate participate in two functions. Both are waste products of metabolism but in the process of elimination contribute to the regulation of the acid-base equilibrium of the body.

THE INGRESS OF WATER AND SALT INTO THE BODY

Water gains entrance into the body in health by way of the upper gastrointestinal tract. It may be ingested as a liquid or as the fluid content of foodstuffs. A small quantity of water in addition is formed within the body daily during the metabolism of foodstuffs. The fluid requirements of persons who live a sedentary life are satisfied ordinarily by the habitual intake of fluid with and between meals. Most persons do not wait until they are thirsty to take liquids but have learned by habit that periodic ingestion keeps them from becoming thirsty. Following inadequate intake of fluid or increased loss from the body, such as is produced by sweating during strenuous exercise, the sensation of thirst appears.

The pathogenesis of thirst has not been decided with finality, but Dill¹ has presented several convincing arguments from the available experimental data. He has concluded that:

Thirst does not necessarily depend on a dry mouth. Thirst without a dry mouth is experienced by man at the evening meal after hard work on a hot day. It is experienced by marine teleosts despite a constantly flowing stream of water through the mouth. Normal dogs without salivary glands do not exhibit unusual thirst.

16. Talbott, J. H.: Interpretations of Clinical Chemical Procedures, Ohio State M. J. 35: 137, 1939.

17. Footnote deleted on proof.

Thirst does not have a single dependence on osmotic pressure of body fluids. A small increase in osmotic pressure produced by ingestion of sodium chloride produces intense thirst, while if the same increase in osmotic pressure is induced by urea the thirst is only moderate.

Thirst does not depend on volume of blood plasma nor of extracellular phase of other tissues. Intraperitoneal injection of glucose solution reduces the volume of the extracellular phase without causing thirst.

Thirst depends on diminished water content and possibly increased osmotic pressure of body cells. While thirst may be somewhat alleviated by rinsing the mouth, it can be satisfied only when water has been delivered by the blood stream to the tissue cells that are demanding it.

The mechanism by which the demand for water makes itself known remains to be elucidated. Contractions of the smooth muscle of the esophagus may be involved.

Thirst is a sensation that man has associated with lack of fluid in the body and usually is satiated by ingestion of water. Thirst associated with dehydration, however, whether in sickness or in health, is probably an index of salt lack as well as fluid lack. Indeed, if dehydration is profound, ingestion of water without sodium chloride does not satiate. The ability to distinguish between desire for water and desire for salt is believed by students of natural history to be highly developed in animals. Man presumably has lost this fine sense of discrimination. It is possible that during the evolutionary era a trick was played on man, since his need for salt is quite as vital as that of animals.

A detailed presentation of the intake of the salts will not be attempted. Except for certain unusual circumstances the requirements of the body should be satisfied by the salts in the diet. This will be considered at length by Icie G. Macy in another article in this series.¹⁸

EGRESS OF WATER AND SALT FROM THE BODY

Fluid is lost from the body in expired air, sweat, gastrointestinal discharges and urine. The losses through the first three channels total approximately 2 liters daily and are essentially beyond voluntary control. The quantity of water which remains for disposal after these requirements have been satisfied is voided by

18. Macy, Icie G.: *The Principal Mineral Elements in Nutrition*, J. A. M. A., to be published.

the kidneys. The kidneys act in this capacity as the buffer organ for excretion of fluid just as interstitial fluid is the buffer compartment for storage of fluid. If an excess of water has been taken into the body, the kidneys are called on to excrete it. If the quantity of body water is less than normal, little or no urine may be voided. The other excretory channels, meanwhile, continue to have their requirements satisfied.

Respiration is a complex mechanism that involves loss of water vapor, gas exchange and regulation of the acid-base equilibrium of the body. The delivery of oxygen to the alveolar spaces and to the circulating hemoglobin in the pulmonary vessels is a vital process. The removal of carbon dioxide occurs simultaneously and permits large quantities of acid to be eliminated.

The concentration of bicarbonate in the acid-base table is given as 25 mEq. per liter of arterial plasma. This is the concentration of carbon dioxide bound to base. An additional small amount, approximately $\frac{1}{20}$ of 25 mEq. per liter, is in solution in the water of the plasma. This is free carbon dioxide, the concentration of which is conditioned by the partial pressure of carbon dioxide in the alveolar air, which is dependent successively on pulmonary ventilation. The sum of free and bound carbon dioxide is known as total carbon dioxide content, the amount obtained from the Van Slyke gasometric determination. The total carbon dioxide content of plasma in healthy persons is of the same order of magnitude as the carbon dioxide combining power. There may be a considerable discrepancy, however, between these values in certain disturbances of acid-base balance. Determination of total carbon dioxide content is to be preferred to determining combining capacity, as it is a more reliable procedure and productive of more information.

The p_H of plasma is dependent on the ratio of free to bound carbon dioxide as well as the total content of carbon dioxide. When this ratio is disturbed, acidosis or alkalosis results. Acidosis, such as is observed in nephritis and in diabetic coma, is associated with a decrease in concentration of total carbon dioxide. This depression is reflected in both free and bound carbon dioxide with a relatively greater effect on the bound fraction. On the other hand, the familiar type of alkalosis which follows the ingestion of alkaline powders

is accompanied by an increased total carbon dioxide content with a relatively greater increase in bound carbon dioxide.

Since the p_H of plasma is determined by the ratio of free to bound carbon dioxide, there are two other possible combinations of acid-base disturbance. Both are relatively uncommon and follow an unorthodox pattern. Hysterical hyperventilation is an example of alkalosis with the total carbon dioxide content of the plasma below normal.¹⁹ Superficially one might expect acidosis with a low carbon dioxide content. The body fluids show increased alkalinity, however, since free carbon dioxide is reduced proportionately more than bound carbon dioxide. On the contrary, with obstruction of the respiratory passages or emphysema an acidosis results. The total carbon dioxide content of the blood, meanwhile, is above normal. The elimination of carbon dioxide from the alveolar spaces is impeded, free carbon dioxide accumulates in the plasma and the ratio is shifted to the acid range.

Sweating, like respiration, is a highly integrated process. The excretion of water in the sweat is necessary for dissipation of heat and maintenance of body temperature. It is expensive for the body, however, because of the seemingly unnecessary loss of salts. The content of sodium and potassium salts in sweat is appreciable, but they serve no known purpose. The sweat glands are developed sufficiently to elaborate a protein free filtrate of plasma, but they cannot produce a salt free filtrate. The concentration of sodium chloride is one-fifth to one-half as great as in plasma. The quantity, however, which may be dissipated daily by profuse sweating is not widely appreciated. Many persons sense that strenuous exercise in a high environmental temperature is accompanied by excessive sweating and salt loss. On the other hand, few persons are aware that a sedentary existence in a hot environment or strenuous exercise in a cold environment may be associated with a dissipation of significant quantities of sodium chloride. If strenuous exercise in a cold environment is undertaken by persons suitably clothed in woollens for protection, sweating is profuse and loss of salt may

19. Talbott, J. H.; Cobb, Stanley; Coombs, F. S.; Cohen, M. E., and Consolazio, W. V.: Acid-Base Balance of the Blood in a Patient with Hysterical Hyperventilation, *Arch. Neurol. & Psychiat.* 39: 973 (May) 1938.

be significant. The matter of sodium chloride deficiency is of concern, therefore, to persons living in cold as well as in warm climates and to members of our armed forces undergoing heavy maneuvers in cold regions as well as in tropical regions.

The volume of sweat lost during eight hours of strenuous work in a hot environment may be as great as 10 or 15 liters, each liter containing as many as 3 or 4 Gm. of sodium chloride. Somewhat smaller amounts may be lost daily by patients with fevers. No ill effects may be attributed to the excessive exchange if amounts lost are replaced periodically. If this is not achieved, symptoms of sodium chloride deficiency may appear. Fluid depletion usually accompanies salt lack, such as in dehydration, but sodium chloride deficiency per se is associated with certain symptoms.

The gradual development of uncomplicated salt deficiency in a sedentary person leads to weakness, excessive fatigue, anorexia and nausea.²⁰ Physical performance is impaired and mental acuity diminished. A thirstlike sensation may appear which is not alleviated by ingestion of fluid. This sensation may be all that remains of the reaction of animals to lack of salt. There is no change in rate of resting pulse, blood pressure or body temperature. The development of many of these symptoms in hot climates has been attributed to some mysterious action of the tropics and has been called tropical languor. Be this as it may, sodium chloride deficiency is a real phenomenon and militates against optimal physical and mental performance.

If salt loss is accompanied by fluid loss, the usual consequence of strenuous activity, muscle cramps and prostration may develop. In previous writings these syndromes have been called heat cramps and heat prostration²¹ because they have appeared usually in persons exposed to high environmental temperatures. With the recent interest in winter sports and the military campaigns of World War II, muscle cramps at least may be observed following strenuous exercise in cold regions as well as in hot regions. A more appropriate title, therefore, might be muscle cramps from salt loss rather

20. McCance, R. A.: Medical Problems in Mineral Metabolism: III. Experimental Human Salt Deficiency, *Lancet* 1: 823, 1936.

21. Talbott, J. H.: Heat Cramps, *Medicine* 14: 323, 1935; III Effects of Heat: *Modern Medical Therapy in General Practice*, Baltimore. Williams & Wilkins Company, 1940, p. 1114.

than heat cramps. A syndrome similar to heat prostration probably is rare in cold environments. It is temporarily incapacitating in hot climates but is not a serious malady. During the 1941 army maneuvers in Louisiana and in the Carolinas several hundreds of soldiers were stricken with this malady. Attention to adequate sodium chloride intake will undoubtedly prevent similar disabilities in actual combat.

Muscle cramps from salt loss are painful spasms of the voluntary muscles and develop in persons engaged in strenuous physical activity. The pathogenesis of symptoms has been shown to be a function of decreased sodium chloride content of the body and not to water intoxication. Susceptibility to cramps varies among persons as well as with the duration of exposure to conditions which induce cramps. Susceptibility may reach a maximum during the first days of excessive sweating before adjustment and acclimation begin to operate. Acclimation is associated with a decreasing concentration of sodium chloride in the sweat, although the volume of sweat excreted may be unchanged. Particular attention should be given to salt intake during the first days of excessive sweating if cramps are to be avoided.

The prevention and treatment of sodium chloride deficiency is theoretically and practically a relatively simple matter. The salt intake should be increased if exposure to high temperatures is anticipated or if physical activity in the cold is contemplated. A daily intake of 15 Gm. of sodium chloride will protect against most symptoms of salt deficiency. Some persons will consume this amount in a high salt diet. Others need extradietary salt as salt tablets or a saline drink. If a central supply of drinking water is available such as in mills, in shops or in army barracks, table salt may be added at some convenient point to make a final concentration of 0.1 per cent. A solution of this low concentration has only a slightly saline taste if it is consumed cool and allays rather than promotes the sensation of thirst. It is thought to be the physiologic way to replace salt lost in the sweat. Since the body has a mechanism for detecting loss of water, i. e. thirst, only sufficient water will be ingested to satisfy this desire. With replacement of water, salt is replaced but only as is needed to restore

amounts lost by sweating. In installations where the general salting of drinking water is not feasible, such as in combat bivouacs, reliance must be placed on salt added to food or contained in salt tablets. A 1 Gm. salt tablet (15 grains) may be taken with each half liter of water or a 0.5 Gm. tablet ($7\frac{1}{2}$ grains) taken with each cup of water. Although these recommendations are applicable to persons excreting excessive quantities of sweat daily, other persons, including those at sedentary jobs, will benefit from an increased salt intake during hot weather. The hazards to be considered from the recommendation on such a broad scale for use of liberal amounts of salt are not believed to be significant. The kidneys are capable of excreting any excess salt ingested except in renal failure and in the presence of edema. Of course if added salt is taken in the drinking water and thirst is allowed to dictate fluid requirements, the salt level in the body is merely maintained and the normal range is never exceeded.

A liberal intake of fluid is imperative for persons subjected to excessive sweating in hot weather. It is needed to provide available quantities for dissipation of heat as well as to maintain the internal environment of the body. The temperature at which water should be consumed may be governed by individual tastes. There is little evidence that cool water by itself is harmful. It has the advantage of a refreshing action in comparison with tepid water. The moderate use of nonalcoholic bottled beverages by adults subjected to considerable physical exercise in the summer is generally considered to be unobjectionable. The belief that an excessively low protein diet is necessary in hot weather is without experimental confirmation. An adequate protein intake (from 60 to 100 Gm. daily), in addition to supplying protein necessary for maintenance of muscle mass, provides more sodium chloride than a low protein intake.

The gastrointestinal tract requires a very small amount of fluid to keep the fecal mass from complete desiccation. Large amounts of fluid may be lost in sickness associated with emesis or diarrhea. Gastric juice contains a great deal of chloride but a relatively low concentration of base. Diarrhea discharges, on the other hand, tend to be alkaline with a preponderance of base, especially potassium.

Lastly, the kidneys excrete the remainder of available fluid after the demands of the lungs, skin and gastrointestinal tract have been satisfied. It is not intended to imply by this statement that this is a haphazard process, for in fact it is a very precise one. The kidneys are the buffer organ for fluid excretion; they also serve as a vital excretory organ for waste products and share with the lungs in the regulation of the acid-base equilibrium. The functions of excretion and acid-base regulation are performed by the nephrons, the functioning units of the kidneys, of which there are more than two million in a normal person. The nephrons are composed of the glomerulus, convoluted and collecting tubule and a blood supply. The afferent arteriole enters the glomerulus, carries blood to the glomerular capillaries for the elaboration of glomerular filtrate, becomes efferent after leaving the glomerulus, continues in intimate contact with the convoluted tubules through a second capillary network, and, after the functions of excretion and reabsorption are performed, becomes a venule. This schematic functioning unit of the kidney as presented by Smith²² is a useful concept, as will be evident in the discussion of the specific duties of water and salt exchange. There is little support for the thesis that individual glomeruli and nephrons are active and inactive periodically or rhythmically. They are probably all working at the same optimum level in health, and what is happening to one is probably an index of what is happening to all. Anatomic and functional changes alter this situation in disease.

Approximately 1.2 liters of whole blood passes through the nephrons each minute. This is called effective renal blood flow²³ and is approximately one third of the total cardiac output. No other tissue of the body save for the lungs claims proportionately as great a volume of blood. The measurement of flow of blood to the kidney whereby this value is derived is an ingenious procedure. If a few cubic centimeters of diodrast, the same preparation used for pyelography, is introduced intravenously, a plasma level of approximately 2 mg. per hundred cubic centimeters may be

22. Smith, H. W.: *The Physiology of the Kidney*, New York, Oxford University Press, 1937.

23. Smith, H. W.; Goldring, W., and Chasis, H.: *The Measurement of the Tubular Excretory Mass, Effective Blood Flow and Filtration Rate in the Normal Human Kidney*, *J. Clin. Investigation* 17: 263, 1938.

achieved. All the diodrast at this plasma level which enters the afferent arterioles of the kidney is removed from the blood in the glomerular and tubular capillary networks. A portion is removed in the glomerular filtrate, the remainder by the excretory activity of the tubules. It is not important in the calculation of renal blood flow to consider the paths of removal from the blood. It must be assumed, however, that diodrast is not altered during its passage through the kidneys and that all the diodrast in renal arterial blood is removed by the nephron before the venule is reached and is excreted immediately into the collecting tubules. If the concentration of diodrast in the blood is determined accurately from a sample of plasma and the amount of diodrast excreted per minute by the kidney is determined by urine analysis, it is possible to calculate renal blood flow. As an example, if the concentration of diodrast in the plasma is 2 mg. per hundred cubic centimeters and 14 mg. of diodrast is excreted per minute into the bladder, then 700 cc. of plasma must have entered functioning nephrons to provide for this quantity of diodrast. The calculation of whole blood flow from plasma flow is possible if the cell volume-plasma volume ratio is determined by the hematocrit reading. If whole blood contains 40 per cent of cells and 60 per cent of plasma, the plasma flow of 700 cc. is only $\frac{60}{100}$ per cent of the total whole blood flow. Therefore $\frac{700}{60} \times 100 =$ approximately 1,200 cc. = renal whole blood flow.

The next step to be considered in an analytic discussion of the elaboration of urine is the formation of glomerular filtrate from a portion of the effective plasma flow. Rate of formation of glomerular filtrate is measured by clearance of inulin or mannitol,²² starchlike polymers. They are not metabolized by the body if injected intravenously and appear unchanged in bladder urine. The path of excretion is exclusively through the glomerular membrane; the tubules neither reabsorb nor excrete either substance. If the concentration of inulin in the plasma is elevated to 100 mg. per hundred cubic centimeters and 125 mg. of inulin is excreted by the kidney into the bladder per minute, 125 cc. of plasma must have participated in the formation of glomerular filtrate to allow this quantity of inulin to be excreted. The rate of formation of glomerular filtrate is therefore

125 cc. per minute. This is characteristic of a healthy man; about one fifth of the effective renal plasma flow is concerned with glomerular filtration.

The formation of glomerular filtrate is the result of the excess hydrostatic pressure in the glomerular capillaries over and above the combined osmotic pressure of the plasma proteins and intraglomerular pressure. Formation of filtrate continues until the osmotic pressure of the plasma, due to concentration of proteins, increases and equalizes the pressure inside and outside the glomerular capillaries. Plasma proteins do not pass through the capillary walls, and a protein free filtrate of plasma is elaborated in the glomerulus. The concentration of electrolytes in glomerular filtrate except for protein is similar to arterial plasma. The qualitative and quantitative integrity of body water is thus maintained. After the formation of glomerular filtrate, the plasma with proteins which have been concentrated nearly 20 per cent flows into the efferent arteriole and subsequently into the contiguous capillary network about the tubule, where the remaining functions of renal activity are performed. Such functions include reabsorption of a large portion of glomerular filtrate, formation of ammonia and elimination of waste products by failure to reabsorb them. Most of the glomerular filtrate is attracted back into the capillary network through the tubular epithelium by virtue of the increase in osmotic pressure of the plasma, which has exceeded the decreased hydrostatic pressure. Approximately 90 per cent of the water and salts of the glomerular filtrate are reabsorbed by this mechanism. Urea, carbon dioxide and phosphate are the principal waste products that are not reabsorbed in proportion to fluid. All except 1 or 2 per cent of the remaining 10 per cent of the fluid of glomerular filtrate is reabsorbed by the tubular epithelium because of the presence of the antidiuretic hormone from the posterior pituitary gland. Only 1 or 2 per cent of the glomerular fluid in healthy persons finally finds its way into the bladder. This seemingly small percentage, however, is sufficient to account for the formation of 2 liters of bladder urine daily. One per cent of 125 cc. equals 1.2 cc. a minute, 70 cc. an hour, and 1,800 cc. in twenty-four hours.

The amount of glomerular filtrate formed is a remarkably constant function under controlled conditions and

is not dependent on amount of fluid available for excretion into the bladder. A normal person with a surface area of 1.72 square meters should form approximately 125 cc. of filtrate a minute in the basal state. The mechanism of the action of the antidiuretic hormone which is responsible for variation in urine output depending on amount of available fluid has been summarized by Verney²⁴ as follows: "The administration of water causes, presumably through the mechanism of the central nervous system, an inhibition of the secretory activity of the pituitary gland. The preformed antidiuretic hormone gradually disappears from the circulating blood, but for a time, about thirty minutes, is present in sufficient concentration to restrain the activity of the kidney. As the concentration of pituitary hormone in the circulating blood diminishes, the rate of urine formation increases to a maximum. When as a result of diuresis much of the water excess is removed, the secretory action of the pituitary gland is resumed and the rate of urine formation diminishes."

The exchange of electrolytes by the kidney follows a channel similar to water. There is no conclusive evidence that any of the electrolytes are excreted by tubular activity. Most of the inorganic bases and acids in glomerular filtrate are reabsorbed to maintain the concentrations in the body. Since sodium and chloride are the predominant electrolytes in plasma, they are the predominant electrolytes in glomerular filtrate. Potassium is present in relatively low concentration in the plasma and may be reabsorbed by different tubular cells than those which reabsorb sodium; at least there is no reciprocal excretion of sodium and potassium by the kidney. On a high potassium intake, several times the quantity of potassium may be excreted in the urine as during a low potassium regimen; the sodium excretion meanwhile undergoes little change.²⁵

Approximately 90 per cent of the sodium (and chloride) in glomerular filtrate is reabsorbed through the tubular epithelium because of the increased osmotic pressure. All of the remainder that is reabsorbed is

24. Verney, E. B.: Die Wasserausscheidung der Säugetierrniere und ihre physiologische Regulation, *Arch. f. exper. Path. u. Pharmacol.* 181: 24, 1926.

25. Talbott, J. H.; Pecora, L. J.; Melville, R. S., and Consolazio, W. V.: Renal Function in Patients with Addison's Disease and in Patients with Adrenal Insufficiency Secondary to Pituitary Panhypofunction, *J. Clin. Investigation* 21: 107, 1942.

subject to hormonal control just as is fluid. Desoxycorticosterone or a similar substance elaborated by the adrenal cortex exercises the control. Other steroids, such as esterone, progesterone and testosterone,²⁶ may participate, but their sodium retaining property is much weaker than that of desoxycorticosterone. In adrenal insufficiency, with inadequate elaboration of cortical hormones, normal quantities of sodium are not reabsorbed by tubular epithelium and a dissipation of this electrolyte in the urine is evident. The action of desoxycorticosterone may be demonstrated in normal persons following an injection of this substance as well as in patients suffering from a deficiency of it.

An important contribution to our knowledge of sodium exchange has been made recently. While retention of pathologic amounts of sodium during the treatment of Addison's disease may follow excessive assimilation of the synthetic hormone desoxycorticosterone, abnormal retention of sodium has never been demonstrated following administration of excessive quantities of cortical extract prepared from animal adrenals. The explanation of this paradox has been presented by Thorn and his associates.²⁷ They have shown that 17-hydroxycorticosterone, one of the active principles in commercial preparations of adrenal cortex extract, has a demonstrable sodium excreting property which may be as potent as the sodium retaining property of desoxycorticosterone. During the use of adrenal cortex extract, the sodium retaining and sodium excreting factors are approximately balanced and edema does not develop. A similar mechanism presumably operates in health to maintain the constancy of sodium in the body.

Phosphate and bicarbonate participate in the regulation of acid-base equilibrium, particularly in the acidification of urine, during their elimination from the body. The reaction of glomerular filtrate is neutral; the reaction of bladder urine is acid. Two functions are achieved in the transformation of neutral glomerular filtrate into an acid urine. Base is retained and acids are lost. It is imperative that available base be retained,

26. Thorn, G. W., and Engel, L. L.: The Effect of Sex Hormones on the Renal Excretion of Electrolytes, *J. Exper. Med.* 68: 299, 1938.

27. Thorn, G. W.; Engel, L. L., and Lewis, R. S.: The Effect of 17-hydroxycorticosterone and Related Adrenal Cortical Steroids on Sodium and Chloride Excretion, *Science* 64: 2441, 1941.

since the body has only a limited supply. All of the inorganic base found in the body is ingested in food and none is manufactured. Acids, on the other hand, are products of metabolism; they are manufactured in large quantities and must be excreted if life is to be maintained. Phosphate contributes to this regulation because it is a trivalent acid. Most of the phosphate (80 per cent) is dibasic at p_H 7.4, the reaction of glomerular filtrate. As the urine becomes acid, it loses its dibasic property and at 4.8 it is present as a monobasic salt. Base is thus conserved, while the quantity of acid which may be excreted is not diminished. Bicarbonate achieves a similar result by allowing base to be reabsorbed by tubular epithelium, leaving high concentrations of carbonic acid available for excretion in bladder urine.²⁸ Yet a third process participates in excretion of acid. This is the formation of ammonia from amino acids in the tubular epithelium. Quantities of ammonia are formed for neutralization of acid substances in health as well as in acidosis, meanwhile allowing inorganic base to be returned to the body.

There are two conditions which illustrate physiologic fluctuations and quasipathologic states of water and salt exchange. These are diuresis and dehydration, respectively. Diuresis is an interesting aberration of renal function which may be induced by an increased intake of fluid or by one of several drugs or chemical substances. Diuretics do not increase appreciably the rate of formation of glomerular filtrate. Some diuretics increase slightly the flow of blood through the kidney, but urine output is not affected by this increase alone. The principal effect is impaired reabsorption of water and salt by the tubules. The osmotic diuretics dextrose, sucrose and urea are present in high concentrations in glomerular and tubular urine and, because of their intrinsic osmotic pressure, they prevent normal reabsorption of water and salt. The xanthine diuretics are quite different chemical substances, although their action on renal exchange is similar to the osmotic diuretics. A small increase in rate of glomerular filtration is overshadowed by a significant depression in reabsorption of tubular urine. The action of the mercurial diuretics

28. Gamble, J. L.: *Clinical Anatomy, Physiology and Pathology of Extracellular Fluid*, Syllabus, Department of Pediatrics, Harvard Medical School, 1941.

is solely on the reabsorptive mechanism; no extrarenal action has ever been demonstrated, nor is there any increase in rate of formation of glomerular filtrate.²⁹

Dehydration may be caused by a number of disturbances and varies in degree from a mild state without detectable clinical signs to alarming severity associated with profound prostration and collapse. Either inadequate intake or excessive loss of water and salt from the gastrointestinal tract or kidneys may be responsible. During the early stages of uncomplicated dehydration there is a diminution in volume of interstitial fluid and plasma, while the composition of plasma with respect to water and salt concentration is maintained. If the disturbance is allowed to progress, interstitial fluid volume and plasma volume continue to decrease, and eventually serious alterations in electrolyte concentrations in the blood may be demonstrated. Serum protein, hematocrit and red blood cell counts are increased, while concentrations of serum sodium and chloride are decreased. If dehydration is complicated by acidosis, such as in untreated diabetes mellitus, the serum bicarbonate is decreased. On the other hand, in dehydration from loss of gastric juice, as in pyloric obstruction, the reaction of the blood is alkaline and the concentration of blood bicarbonate is increased. An increase in concentration of nonprotein nitrogen is a late effect produced by renal failure and by increased breakdown of body protein if supplies of carbohydrate are depleted.

Renal blood flow and formation of glomerular filtrate are unimpaired in the early stages of dehydration. Because of the ability of the human kidney to make a hypertonic urine, nitrogen products continue to be excreted with a very small urine flow while essentially all the sodium chloride is reabsorbed. Compensation cannot be maintained indefinitely as dehydration progresses, and with a decreasing plasma volume renal blood flow diminishes. The viscosity of the blood is increased as the proteins are concentrated; hydrostatic pressure becomes inadequate to form glomerular filtrate and formation of urine ceases. One or more days usually elapses before the appearance of anuria in untreated adults.

29. Coombs, F. S.; Pecora, L. J.; Thorogood, E.; Consolazio, W. V., and Talbott, J. H.: Renal Function in Patients with Gout, *J. Clin. Investigation* 19: 525, 1940.

The treatment of dehydration is not as complicated as the recognition of the several chemical changes. Interstitial fluid has probably suffered the greatest volume change. This can best be restored by physiologic solution of sodium chloride. Such a solution contains relatively more chloride than does plasma or interstitial fluid, but, if the kidneys have not ceased functioning, any excess of chloride is excreted, leaving sodium to combine with carbon dioxide. Acidosis is thereby alleviated. Dextrose may be added to salt solution and is especially indicated if ketosis is present, but it should not be given initially in place of saline solution. Whole blood or plasma is indicated to restore colloid osmotic pressure if blood loss or starvation complicates the clinical state. Profound acidosis should be treated with alkaline solutions in spite of many prejudices which have appeared in the literature condemning them. No harm should result from their judicious use, and less of a burden is put on the kidneys for regulation of acid-base balance of the body. Sodium racemic lactate is very popular in American clinics and has largely replaced bicarbonate solution. One-sixth molar sodium lactate is isotonic and is made by adding one part of molar sodium lactate solution to five parts of sterile distilled water.³⁰ The approximate lactate requirements may be calculated if the level of bicarbonate in the blood is known. As an approximation, 10 cc. of solution per kilogram of body weight is required to raise the carbon dioxide content of the blood 10 volumes per cent. If dehydration is accompanied by alkalosis, saline solution usually suffices. The value of Ringer's and other complex solutions over physiologic solution of sodium chloride in adults is doubtful, although in infants and children replacement of calcium and potassium as well as sodium may be necessary. The intravenous route for parenteral therapy is to be preferred. Subcutaneous infusions are painful and usually unnecessary. Theoretically, parenteral therapy should continue until restoration of water and salt concentrations and restoration of body weight. Practically it is feasible to relax vigilance with partial restoration, and, once the vicious chain of events has been halted, the homeostatic processes of the body are able to act effectively.

30. Hartmann, A. F.: *Theory and Practice of Parenteral Fluid Administration*, J. A. M. A. 103:1349 (Nov. 3) 1934.

CHAPTER VI

PRINCIPAL MINERAL ELEMENTS IN NUTRITION

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DETROIT

In a consideration of the mineral constituents of the body, one should bear in mind that, while these elements constitute only a small portion of the body weight, they enter into all the activities of the body to a much greater degree than their mere weight would indicate. For many years the important dietary components were stated to be protein, fat and carbohydrate, with slight emphasis placed on water and minerals; later, vitamins were added as necessary adjuncts. In the last few years, however, through voluminous records of physiologic investigations, the mineral elements have come into prominence and are now recognized as essential participants in practically every metabolic process carried on by the body.

The brief summary permitted in this presentation forbids reference to many significant studies of mineral metabolism. For the most part, only studies which contain analyses of food, urine and feces for the seven principal minerals will be used as the basis of the present summary and discussion. This should not be interpreted to mean that investigations involving fewer elements have not contributed to a broader understanding and interpretation of the physiologic behavior of the whole group of elements, but reference to all the excellent reports which have appeared is unnecessary, since recently they have been compiled, integrated and interpreted in monograph form by Shohl¹ and ably summarized and cogently reviewed by Sherman.²

For convenience and brevity the discussion is restricted primarily to consideration of the entrance of the principal mineral elements into the body, through the natural foods contained in a well balanced, mixed dietary, their retention and general use in the body

1. Shohl, A. T.: *Mineral Metabolism*, American Chemical Society Monograph Series, New York, Reinhold Publishing Corporation, 1939.

2. Sherman, H. C.: *Chemistry of Food and Nutrition*, ed. 6, New York, Macmillan Company, 1941.

and their exit by way of the urine and feces. Special emphasis is given to the interrelationship of the individual inorganic components in the construction and function of healthy tissue structure in infancy, childhood, adult man, pregnancy and lactation. Discussions of the relative values of different foodstuffs as sources of these nutriment will be covered in chapters dealing with the composition of foods and their nutritive value.

MINERAL COMPOSITION OF THE BODY

A large portion of the ash of the body is composed of calcium, magnesium, sodium, potassium, phosphorus, sulfur and chlorine. As these elements comprise from 60 to 80 per cent of all the minerals contained in the body, they may be considered as representing the principal minerals in nutrition. Table 1 illustrates the mineral content of the whole body at different ages. Aging, up to adulthood, is accompanied by an increase in total ash, an increase in percentage of calcium and phosphorus and a decrease in magnesium, sodium, potassium, chlorine and sulfur. In accordance with Moulton's⁸ prediction on the chemical composition of man, the ash composition at birth represents approximately 3 per cent of the body weight.

Together with protein, fat, carbohydrate, vitamins and other chemical components, the principal minerals are essential to the structure or function of the body at any age or stage of development. Investigators during the past two decades have emphasized the important physiologic role of the principal minerals as individual entities in nutrition and pointed out that through their interrelationship with one another they may have even greater and far reaching significance in the process of life.

Approximately 99 per cent of the calcium,² 70 per cent of the phosphorus and magnesium and some of the sulfur, sodium and chlorine are involved in the construction or functioning of bone, with its cartilaginous organic matrix impregnated with mineral, while considerable quantities of phosphorus, potassium and sulfur are associated with nitrogen in the formation and activities of the muscle, glandular, neural and epithelial tissues. Sodium, potassium and chlorine and to a lesser extent the other elements are held in solution in the

² J. Moulton, C. R.: Age and Chemical Development in Mammals, *J. Biol. Chem.*, 57: 79-97 (Aug.) 1923.

body fluids, giving the intracellular and extracellular fluids their vital dynamic characteristics in the regulation of the p_H of the tissues, secretions and excretions, the osmotic pressure, electroneutrality, the distribution of the minerals in the body through the fluids, the irritability of the nerves and contractibility of the muscles, the permeability of the cells and general metabolism. The proper mixture or balance of the salt solutions in the body is of fundamental importance in maintaining the integrity of function of isolated cells and organs.

FOODS AND FEEDING

In order to meet nutritional needs satisfactorily, the consumption of each essential element must be sufficient to cover body losses and to provide a reserve for the formation of new body tissue when needed

TABLE 1.—*Mineral Composition of the Body**

Age	Body Weight, Kg.	Total Ash, Gm.	Per Cent of Total Ash							
			Ca	Mg	Na	K	P	Cl	S	Total
Fetus, 6 mos.....	0.88	19	28	0.9	10	7	17	8	8	79
Fetus, 7 mos.....	1.16	30	23	0.8	8	7	14	10	6	69
Newborn.....	2.9	100	24	0.7	5	5	14	5	6	60
Adult.....	70	3,000	39	0.7	2	5	22	3	4	76

* Calculated from values given by Shohl.¹

and for the integration of changing physiologic activities in growth and development. Foods vary in composition, the absolute and relative amounts of minerals in different foodstuffs depending on the kind of soil in which they are grown, climatic conditions, water supply and varying degrees of dehydration due to storage and handling. When the determined chemical composition of a number of foods commonly used in the average American diet, from samples collected under carefully standardized conditions at intervals over a period of seven years, were compared with the most recent summary of food values, the percentage differences of the average determined values from the standard tables varied widely: for some elements less than 3 per cent, for others as much as 200 per cent or more.⁴ Because of the variations in the composition of foods and the

4. Hummel, Frances C.; Shepherd, Marion L.; Galbraith, Harry; Williams, H. H., and Macy, Icie G.: Chemical Composition of Twenty-Two Common Foods and Comparisons of Analytical with Calculated Values of Diets, *J. Nutrition* 24:41-56 (July 10) 1942.

differences in food habits of people, the body may not receive the proper quota of nutriments, even though the dietary is adequate according to published standards for food values.

The population may be divided into three groups, the well fed, the underfed and the misfed.

The well fed group receives a diet abundant in quantity and composed of a sufficient variety of foods to encompass all the essential food constituents in ample amounts and in desirable proportions to one another. This dietary meets the requirements of producing and maintaining a nutritionally stable body in the most efficient and satisfactory manner. The best diet need not be the most expensive one, as many of our most common and inexpensive foods possess nutritive superiority. The maintenance of a well balanced dietary from day to day is within the economic resources of every one but requires that foodstuffs be selected carefully, intelligently and thriftily to obtain the recognized essential nutriments in the most abundant amounts and most available form and that they be prepared and served in the manner which best preserves their dietetic value and renders them most easily digested and assimilated. An adequate food mixture which is digested readily and utilized satisfactorily is a prerequisite to buoyant health and nutritive success.

The underfed group takes a diet insufficient in quantity to meet the minimal requirements of the body. Such a diet may result from limited economic resources, ignorance, indifference, disease or personal habits. The misfed group, through indifference, ignorance or faddism, chooses an unbalanced diet that will not permit the desirable synergistic effects of the food components during the physiologic processes of digestion and assimilation and subsequent utilization. The malnourished individual who has been underfed uses larger amounts of nutriments when his diet is improved, while the misfed actually may be inhibited from using certain materials until chemical adjustments have taken place within the tissues to a degree that will permit retention. Successful mineral metabolism, therefore, is conditioned by the absolute quantity of the individual minerals in the diet, the relative proportions among them and the inherent physiologic background and make-up of the person consuming the foods.

THE METABOLIC BALANCE

The term metabolic balance has been applied to the procedure of determining the quantitative intake of a food constituent over a given period of time, the corresponding quantitative outgo of that constituent in the feces and urine, and the calculation of the difference between intake and outgo. This difference is arbitrarily designated by the term retention when the intake is larger than the outgo and loss when outgo is larger than intake. While the metabolic balance procedure is a reliable method for observing the retention of minerals by living subjects, difficulties in interpretation arise from the fact that it is impossible to measure directly the loss of water and chemical substances through the skin, and there is no quantitative method of partitioning the fecal content into the amount representing unassimilated food residue, that which is of bacterial or glandular origin, and the amounts which result from direct excretion of products of metabolism into the intestine. Although all these factors must be recognized, the information obtained from metabolic balance investigation has broad application in nutrition and growth and yields valuable information about physiologic changes that occur with administration of specific dietaries and those that characterize certain pathologic states.

MINERAL METABOLIC BALANCES

With the metabolic balance procedure it is possible to determine with a high degree of accuracy the amounts of the principal minerals in the food, urine and feces. However, the retention values which are calculated by deducting the outgo in urine and feces from the food intake, for a definite period of time, are less accurate, since some of the inorganic elements may be excreted through the skin. The magnitude of this recognized inherent error varies with each element, depending on the amount of cutaneous loss. Recorded in the literature are relatively few metabolic balances which have been obtained on healthy individuals under standardized conditions and include simultaneous determinations of the seven electropositive and electronegative minerals.⁵ Table 2 presents the average daily intakes and retentions

5. Many of the terms used by Shohl² in his attempt to clarify and to use specific terminology in that phase of nutrition dealing with mineral metabolism have been adopted.

of calcium, magnesium, sodium, potassium, phosphorus, chlorine and sulfur, from studies considered comparable for infancy,⁶ childhood,⁷ adult man,⁸ the last six months of pregnancy⁹ and the first three months post partum.¹⁰

Calcium.—This is the element most likely to be deficient in the American dietary.¹¹ The lack of sufficient

6. Swanson, W. W.: The Composition of Growth: II. The Full Term Infant, *Am. J. Dis. Child.* **43**:10-18 (Jan.) 1932. Schlutz, F. W.; Morse, Minerva, and Oldham, Helen: Vegetable Feeding in the Young Infant: Influence on Gastrointestinal Motility and Mineral Retention, *ibid.* **46**:757-774 (Oct.) 1933.

7. The average daily mineral balances have been taken from the mineral balance data recently published (Macy, Icie G.: Nutrition and Chemical Growth in Childhood: I. Evaluation, Springfield, Ill., Charles C Thomas, Publisher, 1942). Since the data were accumulated on 29 healthy children aged 4 to 12 years under comparable experimental conditions during five hundred and ninety-three five day periods (representing two thousand, nine hundred and sixty-five experimental days) they have been used primarily in tracing out the various paths and functions of the individual mineral elements and the total electropositive and total electronegative minerals in metabolism. The subjects received balanced diets containing ample amounts of minerals, vitamins and other essential nutriments. These longitudinal data are more reliable than cross sectional data, since they encompass patterns of increment and rates of growth during consecutive intervals and at different ages. Dearborn and Rothney (Predicting the Child's Development, Cambridge, Mass., Sci-Art Publishers, 1941, p. 147) have estimated that, in the case of standing height, the available longitudinal data on only 248 cases represent the equivalent of cross sectional measurements on 270,000 cases; Wilson (Heights and Weights of Two Hundred and Seventy-Five Public School Girls for Consecutive Ages of 7 to 16 Years Inclusive, *Proc. Nat. Acad. Sc.* **21**:633, 1935) made similar estimates. Indeed, it has been estimated that oxygen consumption and heat production measurements made on each of 10 children once a year for sixteen years, a total of one hundred and sixty observations, would give as much information about the way children grow, or more, than one observation on each of 2,500 children (Talbot, F. B.; Wilson, E. B., and Worcester, Jane: Basal Metabolism of Girls: Physiologic Background and Application of Standards, *Am. J. Dis. Child.* **53**:273-347 [Jan.] 1937). Although the values for the different age groups are indicated in the original (Nutrition and Chemical Growth in Childhood: I), for this discussion I have considered only the average figures for childhood, ages 4 to 12 inclusive; to consider the individual age groups would lead to a consideration of chemical growth, which is the subject of a treatise now in preparation (Macy, Icie G.: Nutrition and Chemical Growth of Children: II. Interpretation, to be published).

8. Clark, G. W.: Studies in the Mineral Metabolism of Adult Man, University of California Publications in Physiology, Berkeley, University of California Press, 1926, vol. 5, pp. 195-287.

9. Coons, Callie M.; Schiefelbusch, Anna T.; Marshall, Gladys B., and Coons, R. R.: Studies in Metabolism During Pregnancy, Experiment Station Bulletin 223, Oklahoma Agricultural and Mechanical College, Stillwater, 1935. Hummel, Frances C.; Hunscher, Helen A.; Bates, Mary F.; Bonner, Priscilla; Macy, Icie G., and Johnston, J. A.: A Consideration of the Nutritive State in the Metabolism of Women During Pregnancy, *J. Nutrition* **13**:263-278 (March) 1937. Hummel, Sternberger, Hunscher and Macy.¹⁰

10. Hummel, Frances C.; Sternberger, Helen R.; Hunscher, Helen A. and Macy, Icie G.: Metabolism of Women During the Reproductive Cycle: VII. Utilization of Inorganic Elements (A Continuous Case Study of a Multipara), *J. Nutrition* **11**:235-255 (March) 1936.

11. Sherman, H. C.: Calcium Requirement of Maintenance in Man, *J. Biol. Chem.* **44**:21-27 (Oct.) 1920. Stiebeling, Hazel K.; Monroe, Day; Coons, Callie M.; Philpard, Esther F., and Clark, Faith: Family Food Consumption and Dietary Levels, Miscellaneous Publication 405, U. S. Dept. Agri., 1941.

TABLE 2.—*Metabolic Balances (Milligrams per Day)*

	Electropositive Minerals						Electronegative Minerals					
	Calcium		Magnesium		Sodium		Potassium		Phosphorus		Chlorine	
	Intake	Reten- tion	Intake	Reten- tion	Intake	Reten- tion	Intake	Reten- tion	Intake	Reten- tion	Intake	Reten- tion
Infancy *.....	721	138	97	8	322	69	1,016	115	558	99	709	108
Childhood †												
4 - 6 yrs.....	841	170	286	44	2,133	206	2,598	182	1,141	156	3,382	250
7 - 9 yrs.....	1,100	168	312	53	2,566	286	3,004	258	1,424	183	3,909	323
10 -12 yrs.....	1,100	300	334	50	3,011	443	3,530	284	1,627	204	4,404	366
Adult man ‡	901	151	284	-19	3,795	1,382	2,486	186	1,492	279	5,073	1,063
Pregnancy §	2,153	453	461	78	4,242	645	4,760	639	2,077	276	5,804	436
Lactation ¶	2,578	-68	525	-10	3,950	334	5,518	526	2,366	-108	6,179	140
											1,210	-16

* First year of life (Swanson.⁸ Schlutz.⁹).† Ages 4 to 12 years (Macy: Nutrition and Chemical Growth in Childhood: I. Evaluation¹).‡ Adult man.⁸§ Last half.⁸¶ First three months (Hummel, Sternberger, Hunscher and Macy.¹⁰ Hummel, Hunscher, Bates, Bonner, Macy and Johnston.⁹ Unpublished). The balances obtained with lactating women are calculated by subtracting from the intake the outgo in urine, feces and breast milk. Only a small number of balances are available, and these demonstrate wide variations in mineral retention, ranging for calcium from an average of 343 mg. daily to an average loss of 480 mg. a day.

quantities of the mineral may have serious consequence on the longevity and fruition of the race.² Ninety-nine per cent of the calcium used by the body is concerned in bone and tooth structure, the remainder with the body fluids and soft tissues. With an average daily calcium intake of 0.72, 0.92 and 0.90 Gm. for infancy (first year of life), childhood (4 to 12 years inclusive) and adult man there were average retentions of 0.14, 0.18 and 0.15 Gm., respectively.

An individual experiencing rapid skeletal growth, having augmented physiologic demands or possessing a subnormal concentration of calcium in the bony tissue may require larger amounts of calcium in proportion to the need to develop a satisfactory physiologic state. Table 2 evidences that the amount of calcium required increases with age, growth and other physiologic demands, that of pregnancy requiring the greatest amount. During the last half of pregnancy, which is generally accompanied by increased food consumption,¹² the calcium retained is used in repleting the maternal bodily stores and in building new maternal tissues, to meet the increasing demands of the parasitic fetus, the losses accompanying parturition, and in preparation of the maternal body to meet postpartum physiologic readjustment and the establishment of milk flow.¹³ A temporary increase in retention may follow an increased intake, whereas a change in dietary calcium to a level lower than before may in itself induce a negative balance. It is known that some of the adult men whose balances are reported were on a low calcium diet preceding the experimental studies;⁸ perhaps this accounts for the comparatively large average daily calcium retention for men.

Individuals vary in their ability to utilize the calcium of their foods. Indeed, Mitchell, Outhouse and their

12. Shukers, C. F.; Macy, Icie G.; Donelson, Eva; Nims, Betty, and Hunscher, Helen A.: Food Intake in Pregnancy, Lactation and Reproductive Rest in the Human Mother, *J. Nutrition* 4: 399-410 (Sept.) 1931.

13. Hunscher, Helen A.: Metabolism of Women During the Reproductive Cycle: II. Calcium and Phosphorus Utilization in Two Successive Lactation Periods, *J. Biol. Chem.* 86: 37-57 (March) 1930. Macy, Icie G.; Hunscher, Helen A.; McCosh, Sylvia S., and Nims, Betty: Metabolism of Women During the Reproductive Cycle: III. Calcium, Phosphorus and Nitrogen Utilization in Lactation Before and After Supplementing the Usual Home Diets with Cod Liver Oil and Yeast, *ibid.* 86: 59-74 (March) 1930. Donelson, Eva; Nims, Betty; Hunscher, Helen A., and Macy, Icie G.: Metabolism of Women During the Reproductive Cycle: IV. Calcium and Phosphorus Utilization in Late Lactation and During Subsequent Reproductive Rest, *ibid.* 91: 675-686 (May) 1931.

co-workers¹⁴ have emphasized that it is as necessary to know how well a person utilizes the calcium of the food which he eats as it is to know the actual calcium content of those foods. They found that preschool children and adults were able to use only one fifth to one fourth of the calcium in milk, but there were variations in the ability of the different individuals to use the calcium supplied. Certain vegetables tend to depress calcium utilization.¹⁵ The presence of vitamins C and D in the diet is essential in calcium utilization; similarly there are optimal levels of phosphorus and fat intakes, in relation to the calcium consumed, which permit the calcium to be more completely utilized.

Calcium is largely excreted through the bowel. In the studies of normal children an average of 13 per cent of the mean daily outgo was eliminated through the kidneys and 87 per cent by way of the bowel. In terms of the calcium intake the mean excretion in urine and in feces amounted to 10 and 70 per cent, respectively, with a retention of 20 per cent. With an average daily intake of 0.92 Gm. (46 milliequivalents) of calcium, 0.74 Gm. (37 mEq.) was excreted by the kidney and bowel and only 0.18 Gm. (9 mEq.) was retained.

Neither the most satisfactory level of calcium intake nor the optimal retention of calcium at any physiologic age or stage of man's development is known. Sherman and his students¹⁶ have shown that the calcium content of rat bodies at various ages was measurably influenced by the level of intake. To what extent such differences exist among human subjects remains to be determined.¹⁷ Perhaps the high vitamin content of the generous mixed dietaries, the healthy condition of the children and well filled body stores of calcium account for the mean daily

14. Steggerda, F. R., and Mitchell, H. H.: The Calcium Requirement of Adult Man and the Utilization of the Calcium in Milk and in Calcium Gluconate, *J. Nutrition* **17**: 253-262 (March) 1939. Kinsman, Gladys; Sheldon, Dorothy; Jensen, Elizabeth; Brenda, Marie; Outhouse, Julia, and Mitchell, H. H.: The Utilization of the Calcium of Milk by Preschool Children, *ibid.* **17**: 429-441 (May) 1939.

15. Shields, J. B.; Fairbanks, B. W.; Berryman, G. H., and Mitchell, H. H.: The Utilization of Calcium in Carrots, Lettuce and String Beans in Comparison with the Calcium in Milk, *J. Nutrition* **20**: 263-278 (Sept.) 1940.

16. Sherman, H. C., and Booher, Lela E.: The Calcium Content of the Body in Relation to That of the Food, *J. Biol. Chem.* **93**: 93-103 (Sept.) 1931. Campbell, H. L.; Bessey, O. A., and Sherman, H. C.: Adult Rats of Low Calcium Content, *ibid.* **110**: 703-706 (Aug.) 1935. Toepfer, E. W., and Sherman, H. C.: The Effect of Liberal Intakes of Calcium or Calcium and Phosphorus on Growth and Body Calcium, *ibid.* **115**: 685-694 (Oct.) 1936.

17. Shohl.¹ Sherman.² Leitch.¹⁸

calcium retention of 7.9 ± 6.8 mg. per kilogram of body weight by the subjects, in contrast to the 10 and 12 mg. estimated by Sherman² Shohl¹ and others.¹⁸ Perhaps the average run of children who grow up under less favorable conditions would need to store 10 to 12 mg. per kilogram daily in order to attain optimal physiologic well-being. An average daily retention of 1 mg. per kilogram of body weight for adult man and 9 mg. during pregnancy are representative of the physiologic performance of the average healthy person.

There are numerous factors influencing the amount of calcium that the body may retain, for example physical and emotional activity, either directly or indirectly reflected through the gastrointestinal tract. Indeed, emotional disturbances may affect the elimination rate of both the kidneys and the bowels.¹⁹ A more rapid laxation rate (bowel movements per day) may stimulate a greater excretion of calcium through the feces.

Phosphorus.—Phosphorus is widely distributed in the body, combined in many forms in soft and hard tissues and associated with protein, carbohydrate, fat, various minerals and organic substances. Seventy per cent of the retained phosphorus combines with calcium, while nitrogen combines with the remaining 30 per cent. Phosphorus is essential in the metabolism of fats and carbohydrates, and participates in many phases of metabolism and in the regulation of the proper hydrogen ion concentration in the tissues, the secretions and excretions of the body. The form in which phosphorus is taken may have an important bearing on its nutritive value in the diet.²⁰

The average daily retention of phosphorus is increased from 99 mg. in infancy to 264 mg. by the twelfth year (table 2). In contrast to the 70 per cent average loss of calcium intake through the alimentary canal, only 31 per cent of the phosphorus intake was lost by that route. Fifty-five per cent of the phosphorus intake was excreted in the urine; 14 per cent was retained. The feces contained 29 to 40 per cent of the phosphorus

18. Leitch, I.: The Determination of the Calcium Requirements of Man, *Nutrition Abstr. & Rev.* 3: 553-578 (Jan.) 1937.

19. Cannon, W. B.: *Bodily Changes in Pain, Hunger, Fear and Rage*, ed. 2, New York, D. Appleton-Century Company, 1936.

20. Sherman, H. C.: Phosphorus Requirement of Maintenance in Man, *J. Biol. Chem.* 41: 173-179 (Feb.) 1920. Lowe, J. T., and Steenbock, Harry: Cereals and Rickets: VII. The Role of Inorganic Phosphorus in Calcification on Cereal Diets, *Biochem. J.* 30: 1126-1134 (July) 1936.

outgo, and the remaining 60 to 70 per cent was lost from the body as metabolites in the urine. In the normal children, with an average daily phosphorus intake of 1250 ± 294 mg. (72.8 mEq.), 684 ± 152 mg. (39.8 mEq.) was excreted in the urine and 393 ± 112 mg. (22.9 mEq.) in the feces; 173 ± 175 mg. (10.1 mEq.) was retained.

Phosphorus is needed in relatively large quantities during growth because it is used so universally in the construction of skeletal, nervous and muscle tissues. Assuming that a relationship exists between body weight and phosphorus retention, during childhood when the average daily phosphorus intake amounted to 55 mg. per kilogram of body weight, the average daily retention was 7 to 8 mg. During periods when the maternal body was being prepared to take care of the increasing demands of pregnancy, parturition and the establishment of lactation, average daily intakes of 36 mg. of phosphorus per kilogram of body weight resulted in average retentions of 4 mg. Adult man consumed, on the average, 11 mg. of phosphorus per kilogram of body weight daily, of which 2 mg. was retained.

The calcium to phosphorus ratio in the food intake has an important bearing on metabolism of both these elements.²¹ Phosphorus fed in excessive amounts causes a corresponding excretion of calcium in the feces; similarly, an increased intake of calcium leads to a greater outgo of phosphorus. On a unit weight basis, with a mean daily calcium:phosphorus ratio of 1:1.4 in the food intake during childhood the mean ratio was 1:7.1 in the urine, 1.6:1 in the feces and 1.0:1 in the retention. For the data compiled from the literature and presented in table 2, the mean calcium:phosphorus ratios for the food intakes and retentions are presented in table 3. Since magnesium may replace some of the calcium required in metabolism, the calcium:magnesium ratios are also given.

Not only is it essential to have liberal amounts of calcium and phosphorus in the diet, but these must be in the proper relationship to one another and be accompanied with a generous supply of vitamin D if skeletal tissue is to be constructed and maintained in a satis-

21. Stearns, Genevieve: The Mineral Metabolism of Normal Infants, *Physiol. Rev.* 19: 415-438 (July) 1939. Shohl,² Sherman,²

factory manner.²² An inadequate and unbalanced diet with respect to calcium and phosphorus may result in rickets in the infant, calcium-poor skeletal growth and possibly rickets in childhood, and osteoporosis or osteomalacia leading to fragility of bones in the adult. The severity of these conditions may be determined chemically by studies of the calcium and phosphorus content of the blood and clinically by roentgenograms of the bones.

Mellanby,²³ Schour and his co-workers²⁴ and Swanson²⁵ in teeth and Sontag²⁶ in the bones of infants have shown that these tissues during formation are extremely sensitive to variations in metabolic processes, the alterations in internal environment of the body being recorded in the incremental layers, or rings, developing at the time. Environmental variations due to disease, to calcium and to vitamin C and D deficient dietaries affect the layers or rings formed at the time they occur. Whether dental caries is related to mineral metabolism remains questionable.²⁷

In general, an increase in calcium intake usually results in increased retention, but by a decreased percentage of the calcium intake retained. The calcium:phosphorus ratio of the retention alters with age; young children retain more calcium in relation to their phosphorus retentions. The calcium:phosphorus ratio in the food also changes, as milk is supplemented with other foods (table 3). The variations in the composition of foods must be recognized, since the interrelationships among the quantities of minerals may be as important as, or more important than the actual amounts of the single elements.

22. Jeans, P. C., and Stearns, Genevieve: *The Human Requirement of Vitamin D*, J. A. M. A. **111**:703-711 (Aug. 20) 1938.

23. Mellanby, May: *Diet and Teeth: An Experimental Study*, Medical Research Council, Special Report Series, No. 191, London, His Majesty's Stationery Office, 1934.

24. Massler, M.; Schour, Isaac, and Poncher, H. G.: *Developmental Pattern of the Child as Reflected in the Calcification Pattern of the Teeth*, Am. J. Dis. Child. **62**:33-67 (July) 1941.

25. Swanson, J. H.: *The Relation of Growth Velocity to the Quality of the Enamel*, J. Am. Dent. A. **18**:2174-2176 (Nov.) 1931; *Age Incidence of Lines of Retzius in the Enamel of Human Permanent Teeth*, *ibid.* **18**:819-826 (May) 1931.

26. Sontag, L. W.: *Evidences of Disturbed Prenatal and Neonatal Growth in Bones of Infants Aged One Month*, Am. J. Dis. Child. **55**:1248-1256 (June) 1938.

27. Boyd, J. D.; Drain, C. L., and Stearns, Genevieve: *Metabolic Studies of Children with Dental Caries*, J. Biol. Chem. **103**:327-337 (Dec.) 1933. Schour, Isaac: *Calcium Metabolism and Teeth*, J. A. M. A. **110**:870-877 (March 19) 1938.

The body may not retain exactly what it needs and reject all other material, for it has great ability, known as homeostasis, to rearrange and adjust materials which it already possesses to meet current needs. An outstanding illustration of this capacity of the body is the mobilization of calcium from the long bones in the healing of rickets and, during gestation, to meet the needs of the fetus. It is obvious that some of the calcium and phosphorus constituting bone must be regarded as a reserve supply of calcium and phosphorus.¹ Moreover, the great flux of minerals in the blood, lymph, intracellular and extracellular fluids and the various secretions, such as saliva, gastric juice, bile and intestinal secretions,

TABLE 3.—*Calcium to Phosphorus and Calcium to Magnesium Ratios **

	Ca : P		Ca : Mg	
	Intake	Retention	Intake	Retention
Infancy... ..	1.3	1.4	7.4	17.2
Children				
4 - 6 years.....	0.7	1.1	2.9	3.9
7 - 9 years.....	0.8	0.9	3.5	3.2
10 -12 years.....	0.7	1.1	3.3	6.0
Adult man.....	0.6	0.5	3.2	...
Pregnancy.....	1.0	1.6	4.7	5.8
Lactation.....	1.1	...	4.9	...

* Based on values in grams.

are in effect mineral reserves. Under conditions of ample intake there is a large storage of calcium during the last three months of pregnancy, but when the diet is inadequate in quantity and quality the demand exceeds the supply, and without the mobile reserves in the maternal bones the fetal demands could not be met.²⁸ Indeed, in many cases in which mothers are either underfed or misfed, both the mother and the fetus suffer severe consequences, depending on the extent of the dietary inadequacy and the degree of maternal reserves present.²⁹

28. Bauer, Walter; Albright, Fuller, and Aub, J. C.: Studies of Calcium and Phosphorus: II. The Calcium Excretion of Normal Individuals on a Low Calcium Diet, Also Data on a Case of Pregnancy, *J. Clin. Investigation* 7: 75-96 (April) 1929.

29. Ebbs, J. H.; Tisdall, F. F., and Scott, W. A.: The Influence of Prenatal Diet on the Mother and Child, *J. Nutrition* 22: 515-526 (Nov.) 1941.

It is now generally recognized that, although the feces do contain some material which has not been absorbed, they also contain material which has been absorbed and subsequently excreted into the alimentary tract. Large quantities of calcium in the food carry through the tract a large portion of the phosphorus which is ingested. A large intake of calcium may, in addition, cause phosphorus which previously has been absorbed, to leave the body by way of the feces rather than in the urine. Excess fat appearing in the feces in the form of soaps may likewise rob the body of calcium and other bases. It has been shown that under some conditions more calcium may be present in the feces than was ingested as food, which proves that some calcium must have been excreted into the intestine. Under long periods of inadequate calcium consumption the homeostatic capacity of the body is brought into play, and the body develops a characteristic ability for conservation of this element in its attempt to maintain physiologic functions compatible with life.³⁰ It is not possible at the present time to decide whether changes in metabolism of certain minerals such as calcium and phosphorus, which result in a greater or smaller amount being present in the serum or deposited in the tissues, depend on more effective absorption, increased excretion or improved deposition in the tissues.

Magnesium.—In certain instances magnesium apparently has the ability to replace some calcium. About three fourths of the magnesium in the body is associated with calcium in skeletal formation, and the remainder is present in the soft tissue and body fluids. Knowledge of its specific function in human nutrition is meager. Perhaps one of its most important functions in the body is serving in combination with organic radicals to form organometallic compounds³¹ which serve as catalysts in physiologic activities. Certainly the actual retention of magnesium by the body at any age is very small (table 2).

Like calcium, magnesium is excreted largely by way of the intestine. With children, of an average daily magnesium excretion of 250 mg. only 35 per cent

30. Nicholls, Lucius, and Nimalasuriya, Ananda: Adaptation to a Low Calcium Intake in Reference to the Calcium Requirements of a Tropical Population, *J. Nutrition* **18**: 563-577 (Dec.) 1939.

31. Gilman, Henry: Some Biological Applications of Organometallic Compounds, *Science* **93**: 47-53 (Jan. 17) 1941.

appeared in the urine and 65 per cent in the feces. Some of the erratic results obtained in metabolic studies may be due in part to unsatisfactory chemical procedures not generally recognized, for iron and other minerals are known to interfere with the accurate determination of magnesium in biologic materials. Using technics assuring accuracy of determination, the mean daily intake of magnesium during childhood amounted to 297 ± 42 mg. (24.4 mEq.), of which 88 ± 18 mg. (7.2 mEq.) and 162 ± 39 mg. (13.3 mEq.) were excreted in the urine and feces, respectively, and 47 ± 47 mg. (3.9 mEq.) was retained. An average of 16 per cent of the intake of magnesium was retained. Assuming a relationship of magnesium retention to body mass, with an average intake of 13 mg. per kilogram of body weight in children, an average daily retention of 2 mg. per kilogram occurred. In pregnancy an average of only 1.3 mg. of magnesium per unit weight was retained, while there was practically an equilibrium in adult man.

Magnesium, calcium and phosphorus balances represent true values, since authoritative evidence³² indicates that no appreciable amounts of these substances are excreted through the skin.

Sulfur.—A nutritionally essential element, sulfur has a far reaching significance in the body. It is a component of glutathione, insulin, thiamine and the organic matrix of the bone. Sulfur and nitrogen metabolism are closely related in protein metabolism. Only two naturally occurring sulfur containing amino acids (cystine and methionine) are known, and they account for a large portion of the sulfur consumed and utilized in the processes of metabolism. In previous studies of sulfur metabolism more emphasis has been placed on the sulfur partition in urine than on the balance between intake and outgo, especially in investigations with children.

In the studies reported for childhood the mean daily sulfur intake was 750 ± 130 mg.; of this amount 79 per cent (593 ± 104 mg.) was lost in the urine, 12 per cent (89 ± 26 mg.) in the feces, and 9 per cent (68 ± 90 mg.) was retained. Wide variations in the metabolism of sulfur are evidenced by the large standard devia-

32. Swanson, W. W., and Iob, L. V.: Loss of Minerals Through the Skin of Infants, *Am. J. Dis. Child.* 45: 1036-1039 (May) 1933. Freyberg and Grant.³³

tion for the retention. These may be attributable to the fact that sulfur exists in several forms in the body, and the retention value includes any cutaneous loss of sulfur, which has been shown to be 60 to 106 mg. of sulfate sulfur daily in adult man.³³

The average daily sulfur retention is increased with age from 8 mg. in infancy to 144 mg. for the 10 to 12 year group. In pregnancy there is an average storage of 205 mg. of sulfur daily, but a loss may occur post partum (table 2). If, in man, one deducts the possible loss of sulfur through the skin, there is still a considerable storage of sulfur. In the men who provided the data considered in this review, nutritional status improved during the investigation;⁸ therefore it is possible that considerable sulfur was used in repair of old and building up of new tissue. It is possible also that there was a greater cutaneous loss of sulfur, since the experimental subjects were quite active during the investigation.

Assuming a relationship between body weight and sulfur retention, with an average daily intake of 34.2 mg. of sulfur per kilogram of body weight at the 4 to 6 year level in childhood, there was a storage of 2.8 mg.; at the 10 to 12 year level, the sulfur intake amounted to 28.8 mg. and the retention 4.1 mg. per kilogram of body weight daily. On a unit weight basis, adult man retained an average of only 1 mg. of sulfur per kilogram of body weight and during the last half of pregnancy the average daily sulfur intake approximated 20 mg. and the average retention 5 mg. per kilogram of body weight daily. Recognizing the possible cutaneous losses, these results are in keeping with our present knowledge of physiologic changes that take place: in normal pregnancy there is building of new tissue in the maternal body, in the enlargement of the uterus, in the mammary glands and in the body generally to take care of the augmented needs during labor and the losses during parturition and during the early days post partum; in lactation there is the physiologic readjustment of the body in the establishment of lactation, accompanied by the losses occurring with the involution of the uterus and other body organs and reserves.

33. Freyberg, R. H., and Grant, R. L.: Loss of Minerals Through the Skin of Normal Humans When Sweating is Avoided, *J. Clin. Investigation* 16: 729-731 (Sept.) 1937.

Potassium.—By virtue of its activity in relation to cellular water, potassium is associated with nitrogen metabolism. When new protoplasmic tissue is being formed, potassium is retained in sufficient quantities to meet the intracellular fluid needs of the newly formed cells. This alkaline mineral is held within the cells, although what activates and regulates its entrance into and its egress from the cells is not completely understood.¹ Irritability of the nervous system is dependent in large measure on the balance between calcium, potassium and sodium ions present in the tissues and the body fluids. A decided decrease in calcium increases irritability, and an increase in potassium will cause a similar effect. The proper mixture or balance among the salt solutions of the body is of fundamental importance for the maintenance of the integrity of function of cells and organs. The mobility and activity of the ions as they participate in the physiologic activity of maintaining electroneutrality and the distribution of minerals in bodily function are covered by another author.

There is an increased storage of potassium as growth proceeds. With average intakes of 1,016 and 2,776 mg. of potassium in infancy and childhood there were mean daily retentions of 115 and 209 mg., respectively (table 2). Both pregnancy and lactation are accompanied by large potassium retention, averaging 639 and 526 mg. daily, respectively. Adult man stores only a small quantity, 188 mg. daily. On a unit weight basis the retentions of potassium for adult man and for women in pregnancy amount to 1 and 9 mg. per kilogram of body weight a day, respectively.

An average of 79 per cent of the intake of potassium was excreted by the kidneys, 13 per cent was excreted by the bowel and less than 8 per cent was retained in childhood. Of the mean daily intake of $2,776 \pm 437$ mg. (71.0 mEq.), $2,191 \pm 405$ mg. (56.0 mEq.) appeared in the urine, 376 ± 136 mg. (9.7 mEq.) appeared in the feces and 209 ± 268 mg. (5.3 mEq.) was retained. The large standard deviations accompanying these values illustrate wide differences in physiologic performance among individuals. The retention, which includes the cutaneous potassium loss, which may reach as much as 30 to 38 per cent, also evidences the approximate nature of these balances. If, however, 30 per cent of the

retention value was lost through the skin, approximately 146 mg. of potassium was retained by the children daily to meet body needs for growth and function.

Sodium.—Although some serves as a part of the structure of the cartilage and muscle cells, sodium is associated with the blood plasma and the extracellular fluids. It functions largely with chloride and bicarbonate in control of the osmotic pressure and ionic equilibrium or electroneutrality of the body fluids and tissues. Considerably more sodium than potassium is needed in the body. The average daily retentions of sodium as determined for infancy, childhood and adult man amounted to 69, 246 and 1,382 mg. daily, respectively. Of the total sodium excretion, 98 per cent may be eliminated in the urine and 2 per cent in the feces. This is to be expected, since sodium is the most predominant positive mineral element in the extracellular fluids, circulates throughout the entire body and serves generally in the metabolic processes of the body in connection with the maintenance of electroneutrality.

The actual requirements of sodium and potassium are comparatively small, but the ratio between these two elements in the diet is considered of great practical importance. The high proportion of potassium to sodium in most common foods introduces two possible dangers, which may be evidenced metabolically by preventing full utilization of the sodium or by causing insufficient assimilation and utilization of other elements, especially calcium and phosphorus. Therefore, to compensate for the excess of potassium over sodium in foods and to enhance palatability, table salt is added to many foods incorporated in the daily diet. The body has a unique ability to conserve sodium in times of shortage and to absorb and distribute sodium rapidly when it is introduced into the body.

The mean daily intake of sodium by 29 children averaged $2,310 \pm 368$ mg. (100.5 mEq.), of which 787 mg. was given in chemically pure sodium chloride. The average daily excretion of sodium in the urine amounted to $2,022 \pm 377$ mg. (88.0 mEq.), while a small but significant quantity (42 ± 39 mg., or 1.8 mEq.) was eliminated through the alimentary canal, and 246 ± 280 mg. (10.7 meq.) was retained. Assuming

that 12 per cent of the retained sodium was dissipated through the skin,³³ the true mean daily retention of the children was 216 mg.

Chlorine.—A component of all body secretions and excretions, chlorine is stored only to a limited extent, in the skin and subcutaneous tissue and in the skeleton. The chlorides of the blood, particularly sodium chloride, compose about two thirds of the blood anions. They play an essential role in maintaining electroneutrality within the body and serve in large measure to maintain the osmotic pressure of the extracellular fluids. Gastric secretion contains chlorine in free hydrochloric acid and combined in salts. Chlorine, like sodium and potassium, is lost through the skin to the extent of about one fifth of that retained;³² hence the retentions in the metabolic balances presented in table 2 are exaggerated by that amount.

The average daily retentions of chlorine for infants, children and man amount to approximately 108, 277 and 1,063 mg., respectively. Ninety-one per cent of the chlorine intake is eliminated through the urinary tract and only 1 per cent through the bowel. In children whose sodium chloride intake was controlled, the mean daily chlorine intake was $3,596 \pm 460$ mg. (101.4 mEq.), of which $3,265 \pm 467$ mg. (92.1 mEq.) was excreted in the urine, 54 ± 33 mg. (1.5 mEq.) was excreted in the feces and 277 ± 241 mg. (7.8 mEq.) was retained. Assuming that one fifth of the retention value represents cutaneous losses, the true retention value would be 222 mg. of chlorine per day.

Human dietaries usually contain considerable quantities of sodium, potassium and chlorine and it is only during diarrhea, excess sweating and certain endocrine disturbances and metabolic conditions that an additional intake of these elements is required. Under ordinary conditions the body can adapt itself to shortages of these elements,³⁴ and it is generally assumed that a diet which is adequate in all other respects will contain amounts sufficient to meet the nutritive demands. It is recognized, however, that the adjustment of the body to a change in level of intake of sodium, and of potassium in particular, requires longer than the conventional week or ten days, and that excessive proportions of

34. Osborne, T. B., and Mendel, L. B.: *The Inorganic Elements in Nutrition*, J. Biol. Chem. **34**: 131-139 (April) 1918.

potassium in diets may prevent full utilization of sodium by the organism and may cause insufficient utilization of calcium and phosphorus.

Minerals are lost from the body during acidosis. The growing child is particularly prone to acidosis, especially when consuming high fat diets. In a controlled metabolic balance study which included the determination of the seven positive and negative minerals and nitrogen Sawyer, Baumann and Stevens³⁵ observed 2 children aged 5 and 8 years during the consumption of a normal diet and subsequently when the lactose and sugar of the normal period were replaced by an isodynamic quantity of pure butter fat, the mineral, nitrogen and calory intakes remaining the same during the two observation periods. The high fat diet caused increased acid production in the body, which resulted in increased elimination of nitrogen, sulfur, calcium, magnesium, phosphorus, sodium, potassium and chlorine. It is assumed that the nitrogen and sulfur were derived from catabolized muscle; calcium, phosphorus and magnesium were of skeletal origin, and sodium, chlorine and potassium were obtained from body fluids. The losses, particularly calcium and phosphorus, varied directly with the severity of acidosis.

POSITIVE AND NEGATIVE MINERAL BALANCES

The electropositive minerals (calcium, magnesium, sodium and potassium) and electronegative minerals (phosphorus, sulfur and chlorine) serve singly and in combination in the physiologic structure and function of the body. As food burns in the body, the organic anions, citrates, acetates and so on are completely oxidized, all of the positive mineral elements and the negative element chlorine are released, and the negative minerals sulfur and phosphorus are generally assumed to be completely oxidized to phosphates and sulfates. However, the anion values of sulfur and phosphorus retained in the body may have several valences, since they enter into combination with other elements to form many different compounds. In calculating, the average valence of 1.8 has been assigned to phosphorus and a valence of 2 to sulfur.³⁶

35. Sawyer, Margaret; Baumann, L., and Stevens, F.: *Studies of Acid Production: II. The Mineral Loss During Acidosis*, *J. Biol. Chem.* **33**: 103-109 (Jan.) 1918.

36. Shohl,¹ Sherman.²

During growth and body repair there is an accumulation of both positive and negative minerals in the tissues, the total amount depending on the intensity of the physiologic processes. The relationship between the gross amounts of positive and negative minerals retained is determined by the relative demands for materials with which to construct hard and soft tissue and by the cutaneous losses of potassium, sodium,

TABLE 4.—*Metabolic Mineral Balances** (Milliequivalents per Day)

	Total Positive Minerals		Total Negative Minerals		Total Minerals		Excess Positive Minerals	
	Intake	Retention	Intake	Retention	Intake	Retention	Intake	Retention
Infancy.....	84	13	62	9	146	22	22	4
Children								
4 - 6 yrs.....	225	26	204	20	429	46	21	6
7 - 9 yrs.....	269	32	245	24	514	56	24	8
11-12 yrs.....	303	45	282	35	585	80	21	10
Adult man.....	297	72	287	58	584	130	10	14
Pregnancy.....	452	73	353	41	805	114	99	32
Lactation †.....	485	24	387	-3	872	21	98	27
Average Daily per Kilogram of Body Weight								
Children								
4 - 6 yrs.....	11.2	1.3	10.2	1.0	21.4	2.3	1.0	0.3
7 - 9 yrs.....	10.1	1.2	9.2	0.9	19.3	2.1	0.9	0.3
11-12 yrs.....	8.6	1.3	8.0	1.0	16.6	2.3	0.6	0.3
Adult man.....	2.1	0.5	2.0	0.4	4.1	0.9	0.1	0.1
Pregnancy.....	7.2	1.0	5.8	0.6	13.0	1.6	1.4	0.4
Lactation †... ..	8.3	0.5	6.7	- 0.02	15.0	0.5	1.6	0.5

* A valence of 1.8 has been used for phosphorus and 2 for sulfur, although it is recognized that these are only approximations. No deductions have been made for cutaneous losses.

† Retentions were calculated as intake minus outgo in urine, feces and breast milk.

chloride and sulfur. Table 4 presents the average intakes and retentions of the total positive minerals, total negative minerals, total positive plus negative minerals and excess of positive minerals for infancy, childhood, adult man, pregnancy and lactation.

Skeletal tissue synthesis creates a demand for positive minerals; soft tissue construction requires a preponderance of negative minerals; therefore increased retentions of positive minerals in relation to negative minerals indicates an impetus to skeletal construction.

and the reverse shows an emphasis on soft tissue formation. The retention of positive, negative and total minerals is increased from infancy through childhood to adulthood, but the average daily retentions per kilogram of body weight decrease. While pregnancy demonstrates augmented metabolic demands for all minerals, metabolic balances concurrent with early lactation may demonstrate a loss of negative minerals commensurate with the tissue involution taking place in the uterus and other maternal organs and the peculiar physiologic demands of lactation. When considered on a unit weight basis, growth and pregnancy are accompanied by a retention of total minerals and excess positive minerals, but during lactation these occur to a lesser extent than in adult man. A retention of total minerals is one of the best criteria that growth, repair or repletion are taking place.

The positive and negative minerals constitute approximately 25 per cent of the total urinary solids of children. Although the diet may be constant in quantity and quality, the amounts of positive and negative minerals excreted from day to day depend on current metabolic demands for growth or maintenance. An average of 156 mEq. of mineral cations and 169 mEq. of mineral anions were excreted in urine by normal children. These, together with the non-mineral cation NH_4^+ , the titrable acidity and the organic acids, determine the acidity or alkalinity of the urine. In the feces of the children, the positive and negative minerals together composed approximately 10 per cent of the total fecal solids. An average of about 7 per cent of the total weight of the fecal solids consisted of positive minerals. Calcium, magnesium, potassium and phosphorus compose the greater part of the minerals eliminated in the feces, but relatively small amounts of sodium, sulfur and chlorine are present.

The electropositive minerals (calcium, magnesium, sodium and potassium) are especially important in skeletal formation, particularly calcium and magnesium, in nervous and muscular activity and blood coagulation. Sodium and potassium participate in the control of body water as well as in other structural and functional activities. In childhood the average daily positive mineral content of the diets was 242 ± 40 mEq., of which

29 ± 22 mEq. was retained. The average daily positive mineral content of the feces was 57 ± 14 mEq., 56 per cent of which was calcium. The average daily consumption of positive minerals per kilogram of body weight was 10.7 ± 1.6 mEq. On the same basis 6.9 ± 1.0 mEq. was excreted in the urine, 2.5 ± 0.7 mEq. was eliminated in the feces and 1.3 ± 0.9 mEq. was retained.

The average daily intake of electronegative minerals (phosphorus, sulfur and chlorine) in childhood was 221 ± 37 mEq., of which the kidneys excreted 169 ± 26 mEq. and the intestine 30 ± 8 mEq., while 22 ± 20 mEq. was retained. Approximately 85 per cent and 15 per cent of the excretion of the negative minerals take place in the urine and feces, respectively, in comparison to 73 per cent and 27 per cent, respectively, for the excretion of positive minerals. On the basis of body weight an average of 9.8 ± 1.4 mEq. of total negative minerals was consumed and only 1.0 ± 0.8 mEq. was retained per kilogram daily.

EXCESS MINERALS

When the quantity of positive minerals exceeds the quantity of negative minerals or the negative exceeds the positive, the excess for the food intake is designated by the terms alkaline-ash and acid-ash value, respectively; for the urine and feces the values are given as the excess of positive or negative minerals. The alkaline-ash values of the diets and the excess positive minerals retained by infants, children, man and pregnant and lactating women are shown in table 4, daily and daily per kilogram of body weight. All diets had an alkaline-ash value, though that of adult man was lowest (10 mEq.). The value for the diets of infants and children ranged between 21 and 24 mEq., and in pregnancy and lactation the amounts were 99 and 98 mEq. daily. A retention of cations in excess of anions occurred at all ages; on a unit weight basis there was an average daily retention per kilogram of 0.3 mEq. for childhood, 0.1 mEq. for man, 0.4 mEq. for pregnancy and 0.5 mEq. for lactation.

Retentions of both positive and negative minerals are essential to growth. Normally the body requires a very slight excess of total positive over total negative minerals, but greater excess positive mineral retentions indicate an emphasis on skeletal growth or an augmen-

tation of mineral storage in bony tissue. Retention from the dietary of an excess of negative minerals indicates that formation of muscular, glandular and neural tissues is proceeding at the faster rate.

The amount stored of any one or all of these inorganic elements is influenced by the composition of the food and the current nutritive needs of the individual. The amount of each element ingested, the proportion of one element to another, the fat and other components of the diet—all are determining factors in metabolism and utilization of the positive and negative minerals. Indeed, the proportions of individual members of the positive and negative mineral groups in the diet may have more importance in general metabolism during growth than the total or excess quantities of the two groups of elements.³⁷

Some foods or conditions may cause a change in the path of excretion from urine to the feces; that is, an increased output of calcium in the feces may be compensated by a decrease in output of calcium in the urine. The mineral elements which seem to be most susceptible to exchange between the urine and feces are calcium, phosphorus, sodium, potassium and chlorine. Cutaneous losses of potassium, sodium, chlorine and sulfur may cause a significant cumulative error in the retention values. With proper recognition of these possible inherent errors, metabolic balance data including the quantitative chemical determination of the positive (calcium, magnesium, sodium, potassium) and negative minerals (phosphorus, sulfur, chlorine) in the food over a given period of time, and the quantitative outgo of these constituents in the feces and urine, give valuable information concerning the physiologic activity in the body. The calculation of the difference between intake and outgo in the urine and feces, although in some cases it may be of an approximate nature, gives significant information on the metabolism of the individual elements and groups of minerals during the various stages of growth and physiologic function and render valuable service in the diagnosis and treatment of certain types of diseases.

37. Macy, Icie G.; Hummel, Frances, C.; Hunscher, Helen A.; Shepherd, Marion L., and Souders, Helen J.: *Effects of Simple Dietary Alterations on Retention of Positive and Negative Minerals by Children*. *J. Nutrition* 19: 461-476 (May) 1940.

CHAPTER VII

IRON IN NUTRITION

REQUIREMENTS FOR IRON

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In spite of evidence to the contrary, the idea is still current that when the diet is deficient in iron the red cells soon become deficient in hemoglobin (hypochromic) and smaller (microcytic) than normal. This idea is certainly not true for the healthy adult male or for healthy women after the menopause. It may sometimes be true for growing children and for women during their menstrual life or during pregnancy, or for any person who has lost or is losing considerable amounts of blood from some lesion of the body. Much remains to be learned about the metabolism and functions of iron, but there is strong evidence that a diet deficient in iron will not produce iron deficiency except in the presence of increased needs for iron such as growth, pregnancy or blood loss.

One basic fact is essential in any adequate consideration of iron deficiency: iron is an element and, unlike certain organic substances of the food which are necessary to the body, such as the vitamins, it is not destroyed or used up in the body but is conserved and, if not excreted, can be utilized again and again. Another important fact concerning iron is that it is not excreted by either kidney or intestinal tract in appreciable quantities. It has been called a "one way substance;" that is, it may be absorbed, or if not absorbed it will be eliminated in the stools, but, in any ordinary sense it is not excreted. The iron content of the normal human urine is very small. Lintzel¹ regarded it as negligible, less than 0.02 mg. per liter. Marlow and Taylor² found values for urinary iron ranging from 0.03 to 0.8 mg. in twenty-four hours. Lanyar, Lieb and Ver-

1. Lintzel, W.: *Neuere Ergebnisse der Erforschung des Eisenstoffwechsels*, *Ergebn. d. Physiol.* **31**: 844, 1931.

2. Marlow, Arthur, and Taylor, F. H. L.: *Constancy of Iron in the Blood Plasma and Urine in Health and in Anemia*, *Arch. Int. Med.* **53**: 551 (April) 1934.

dino³ found less than 0.01 mg. of iron per liter of urine. The iron of the urine is not increased significantly even after destruction of the red blood cells by phenylhydrazine.⁴ It may be increased immediately after the administration of inorganic compounds parenterally.⁵ Hahn and his associates,⁵ in a study of dogs which were given radioactive iron as ferrous gluconate by vein, found an extra output of iron in the urine and feces for a few days after its injection (2 to 8 per cent of the total amount injected). Following this the urinary iron dropped to traces, but the stools contained from 0.05 to 0.4 mg. of radioactive iron daily. The bile contained insignificant amounts of iron, which confirms the findings of others. The authors considered the evidence conclusive that the dog excretes iron only with difficulty and in small amounts. Maddock and Heath⁶ decided from microscopic study of the gastrointestinal tract and of colonic explants on the abdominal walls of dogs before and after the administration of iron that this metal cannot be observed to be excreted by these organs. McCance and Widdowson^{6a} concluded that the power of the intestine to excrete iron has been greatly exaggerated.

Studies of the balance between the iron ingested and the iron contained in the urine and feces indicate no excess of the latter over the former (negative balance) and indeed there is a necessary positive balance in the case of children and pregnant women. This is illustrated in the summary shown in table 1. An exception is the case of the two fasters Cetti and Breithaupt. Here, however, the experimental periods were short, the methods probably faulty, and the conditions of fasting are in no way comparable to ordinary nutritional circumstances. Particular note should be made of the

3. Lanyar, F.; Lieb, H., and Verdino, A.: Ueber die Ausscheidung von Eisen im menschlichen Harn unter physiologischen und pathologischen Verhältnissen, *Ztschr. f. physiol. Chem.* **217**: 160, 1933.

4. Reznikoff, Paul; Toscani, Vincent, and Fullarton, Ruth: Iron Metabolism in a Normal Subject and in a Polycythemic Subject, *J. Nutrition* **7**: 221 (Feb.) 1934. Barer, Adelaide; Paul, W. D., and Baldrige, C. W.: Studies on the Relationship Between Oxygen Consumption and Nitrogen Metabolism: III. Polycythemia Vera, *J. Clin. Investigation* **13**: 15 (Jan.) 1934. Hahn, Bale, Hettig, Kamen and Whipple.⁵

5. Hahn, P. F.; Bale, W. F.; Hettig, R. A.; Kamen, M. D., and Whipple, G. H.: Radioactive Iron and Its Excretion in Urine, Bile and Feces, *J. Exper. Med.* **70**: 443 (Nov.) 1939.

6. Maddeck, Stephen, and Heath, C. W.: Is Iron Excreted by the Gastrointestinal Tract of the Dog? *Arch. Int. Med.* **63**: 584-589 (March) 1939.

6a. McCance, R. A., and Widdowson, E. M.: Absorption and Excretion of Iron, *Lancet* **2**: 680, 1937.

TABLE 1.—*Summary of Studies on Iron Metabolism*
(From Heath and Patek⁷)

Authors	Conditions	Daily Intake of Iron, Mg.	Daily Output of Iron, Mg.	Daily Iron Balance, Mg.
Josephs, H. W.: Bull. Johns Hopkins Hosp. 55: 259, 1934	Normal infants; milk diet	—0.01
	(1) Birth to 2 months.....	+0.12
	(2) 2 months to 4 months.....	+0.18
	(3) 4 months to 6 months.....	+0.18
Wallgren, A.: Rev. franç. de pédiat. 9: 196, 1933	5 normal infants aged 3 weeks to 11 months; breast milk
Aescham, L.: J. Nutrition 10: 337, 1935.....	6 preschool children, weight 17.1 to 19.3 Kg., 90 experimental days	10.67	9.41	+1.26
Lehmann and Flor: J. Nutrition 5: 141, 1932.....	4 children aged 35 to 56 months
	20 experimental days.....	3.25	2.07	+1.19
	20 experimental days.....	6.50	3.50	+3.21
	8 children aged 8 to 6 years; 80 experimental days	10.89	7.81	+3.08
Daniels and Wright, <i>ibid.</i> 8: 125, 1934.....	Children aged: 4.....	7.95	7.07	+0.88
	5.....	7.75	7.18	+0.62
	6.....	8.17	7.96	+0.19
	8.....	8.53	7.04	+1.14
	9.....	11.16	8.68	+2.48
	10.....	11.80	8.68	+3.12
	12.....	12.18	9.19	+2.99
Farrar and Goldhamer: J. Nutrition 10: 241, 1935.....	Normal man.....	5.2	5.4	—0.2
	Normal man.....	7.7	7.8	—0.1
	Man; minimal tuberculosis.....	7.3	7.4	—0.1
	Normal woman.....	8.3	8.2	+0.1
	Middle aged man, recovered from deficiency syndrome; 132 experimental days	18.4	12.8	+5.6
Bernikow, Toscani and Fullerton *.....	3 normal women; 56 experimental days	13.76	14.96	—1.17
	4 normal women; 440 experimental days.....	11.81	11.12	+0.69*
Ohlsen and Daum: J. Nutrition 9: 75, 1935.....	Normal men: (1) 16 experimental days.....	58.5	58.2	+0.3
Leverton and Roberts, <i>ibid.</i> 13: 65, 1937.....	(2) 49 experimental days.....	12.7	12.8	—0.1
Lintzel: Ztschr. f. Biol. 89: 342, 1929.....	(3) 16 experimental days.....	2.5	2.4	+0.1
	(4) 3 experimental days.....	0.9	0.9	0.0
Coons: J. Biol. Chem. 97: 215, 1932.....	9 women, from eleventh week of pregnancy to term	14.72	11.66	+3.16
Lehmann, Mueller, Munk and Senator: Virchows Arch. f. path. Anat. 131, supp. 1, 1893	Stool examinations on two fasting men: (1) Cetti, 10 days.....	0	7.3	—7.3
	(2) Breithaupt, 6 days.....	0	8.0	—8.0

* After blood loss from menses and venesection was taken into consideration, the subjects were approximately in iron balance.

observations of Lintzel. In his experiments even when the diet contained as little as 0.9 mg. of iron daily, the caloric intake being adequate, iron balance was reached within a few days.

To the evidence of the chemical and microscopic studies which show meager iron excretion from the body may be added the evidence from certain clinical observations. Study of patients having hypochromic anemia which is alleviated by iron medication shows that serious blood loss can usually be demonstrated in such patients. In so-called idiopathic hypochromic anemia, careful clinical study of cases has shown the wide prevalence of abnormal blood loss, usually from menorrhagia or bleeding hemorrhoids and often occurring in a subtle and chronic form.⁷ The evidence is so overwhelming that iron deficiency occurring in men and women is associated with abnormal blood loss that, even in the presence of very poor diets and conditions of the gastrointestinal tract which interfere with the absorption of iron, a history of blood loss in such cases is always to be expected and should be most carefully searched for. I have not yet observed such a case which I felt could reasonably be supposed to have resulted from a prolonged negative iron balance.

In contrast to the very small amounts of iron which are lost from the body by the renal and gastrointestinal routes are the significantly large amounts of iron which may sometimes be shown to be absorbed. The metabolism experiments of Fowler and Barer⁸ and of Brock and Hunter⁹ show that an astonishingly large amount of iron may be retained by the body. Retention of over 6 Gm. of iron in an experimental period has apparently been demonstrated: more than the amount of iron assumed to be present normally in the body. That the body in certain cases can retain large amounts of iron is demonstrated in hemochromatosis, in which over 50 Gm. of iron may be recovered from the tissues. In this disease there may be disturbance of a control mechanism which limits the retention of iron in normal individuals. In dogs and in man it has been demon-

7. Heath, C. W., and Patek, A. J.: The Anemia of Iron Deficiency, *Medicine* **16**: 267-350 (Sept.) 1937.

8. Fowler, W. M., and Barer, A. P.: Iron Retention Following Use of Ferric Ammonium Citrate in Hypochromic Anemia, *J. A. M. A.* **104**: 144, 1935.

9. Brock, J. F., and Hunter, D.: The Fate of Large Doses of Iron Administered by Mouth, *Quart. J. Med.* **6**: 5, 1937.

strated that iron is retained in larger amounts when there is need for materials for blood regeneration.¹⁰ The iron is apparently absorbed largely in the upper small intestine and perhaps in the stomach.¹¹ It is conveyed in the plasma, possibly also in the red blood cells and is found stored particularly in the liver, spleen, kidneys, skin and apparently the bone marrow. In persons in good nutrition there is presumably a store of such iron which is available should a need arise, for example the need occasioned by acute blood loss.

Although it cannot be said that adult man will become anemic if his diet contains too little iron, much can be said in favor of diets containing adequate amounts of iron for the population at large. Blood loss of one sort or another is extremely common, particularly in females, and adequate stores of iron should be available in the body to meet such demands when they arise. Sherman¹² has estimated the "dietary standard" of man as about 12 mg. of iron daily. I estimated the diets of over 200 healthy male college undergraduates to contain an average of 16 mg. of iron a day and to vary from 6 to over 20 mg. of iron a day. The Committee on Food and Nutrition of the National Research Council¹³ has recommended the daily allowances for iron given in table 2.

The need for iron varies greatly at different ages and under different conditions. In growth there is a need for iron to supply the hemoglobin in the expanding blood volume. In fact, by far the greater part of the functioning iron of the body is located in the circulating hemoglobin. The blood under ordinary conditions contains more than five times the concentration of iron of any organ of the body, and its mass is considerably

10. Fontès, G., and Thivolle, L.: Bilan du fer chez le chien rendu anémique par saignées répétées, *Comptes rend. Soc. de biol.* **109**: 911, 1932. Moore, C. V.; Roberts, H. R., and Minnick, Virginia: A Study of the Selective Absorption of Iron with the Aid of Its Radioactive Isotope, *J. Clin. Investigation* **20**: 436-437 (July) 1941. Ross, J. F., and Chapin, M. A.: The Selective Absorption of Radioactive Iron by Normal and Iron Deficient Human Subjects, *ibid.* **20**: 435 (July) 1941.

11. Hahn, P. F.: The Metabolism of Iron, *Medicine* **16**: 249-266 (Sept.) 1937. Hahn, P. F.; Bale, W. F.; Lawrence, E. O., and Shipple, G. H.: Radioactive Iron and Its Metabolism in Anemia: Its Absorption, Transportation and Utilization, *J. Exper. Med.* **69**: 739 (May) 1939. Arrowsmith, W. R., and Minnich, Virginia: Site of Absorption of Iron from the Gastrointestinal Tract, *J. A. M. A.* **116**: 2427 (May 24) 1941.

12. Sherman, H. C.: *Chemistry of Food and Nutrition*, ed. 5, New York, Macmillan Company, 1937.

13. Recommended Daily Allowances for Specific Nutrients, *J. A. M. A.* **116**: 2601 (June 7) 1941. (See page 335).

larger than that of the liver.¹⁴ Growth of the blood volume can be placed beside loss of blood as an important contributing cause of iron deficiency. At puberty as well as in infancy there is an acceleration of growth and an increase in the circulating hemoglobin. At puberty in girls there is also a loss of hemoglobin (and therefore of iron) in the menstrual fluid. In pregnancy there is an increased need for iron to supply the growing fetus. The child at birth normally has a certain amount of stored iron, both in the tissues and in the excess circulating hemoglobin, which is available for use. In prematurity and twin births this may be considerably limited and these infants are later vulnerable to iron deficiency. Finally, during lactation there is loss of iron which annually probably is similar in quantity to the menstrual loss. Unless iron is provided to replace what is lost or to build new hemoglobin under these conditions, iron deficiency anemia will manifest itself. Sufficient stored iron will, of course, provide the necessary iron. But, if the stores of iron are insufficient, iron must be provided through the food or through medication, if iron deficiency anemia is to be avoided. Sometimes gastrointestinal disturbances such as diarrhea, achlorhydria or intestinal disease interfering with absorption will prevent iron from entering the body, even though the diet has supposedly adequate amounts of iron. When this is the case an individual may maintain a low hemoglobin level for many years. The administration of large doses of inorganic iron in such cases will practically always relieve the anemia.

Tables 3 and 4 give the estimated annual iron requirements for physiologic needs of males and females and the data from which these requirements are derived. The sources for the changes of growth, blood volume and hemoglobin values with age and sex have been described in the original publication of the tables.¹⁵ A somewhat similar analysis of the growth requirement for iron has been reported by the White House Conference on Child Health and Protection.¹⁶ The figures

14. In any anemic state there is a diminution of the gross amount of circulating hemoglobin and also of the circulating iron. This does not mean that iron deficiency is present in all kinds of anemia. In pernicious anemia, for example, there is usually an adequate amount of stored iron which is available for blood formation when liver extract (without iron) is given.

15. Heath and Patek,² pp. 278-283.

16. Growth and Development of the Child: Part III. Nutrition (White House Conference on Child Health and Protection), New York & London, Century Company, 1932.

in that report are somewhat higher, being based on the total iron content of the body. Tables 3 and 4 show that iron requirements are greatest in infancy and early childhood and about the age of puberty, and they are larger in females than males after puberty and are increased during pregnancy. At these times and under these conditions iron deficiency is seen most commonly, if we except cases of pathologic blood loss. This supports the assumption which has been made that, if physiologic needs for iron are not supplied, iron deficiency anemia will occur.

Since the physiologic factors which favor iron deficiency are universal, as well as blood loss from wounds

TABLE 2.—*Recommended Daily Allowance for Iron*
(Committee on Food and Nutrition, National Research Council)

	Iron, Mg.
Children under 1 year	6
Children 1-3 years.....	7
Children 4-6 years.....	8
Children 7-9 years.....	10
Children 10-12 years.....	12
Girls 13-15 years	15
Girls 16-20 years.....	15
Boys 13-15 years.....	15
Boys 16-20 years.	15
Women, nonpregnant.....	12
Women, pregnant.....	15
Men.....	12

or lesions of disease, there can be no purely geographic distribution of iron deficiency. There are, however, environmental factors which may render iron deficiency more common in certain locations. The anemia associated with hookworm infection is an anemia of iron deficiency and is found in tropical and subtropical climates. Customs restricting the activities of women, such as those of certain sects of India, may interfere in various ways with the intake of food iron. It is probable that Victorian influences circumscribing the activities of women were in part responsible for the high incidence of "chlorosis" in the past century.¹⁷

17. Davidson, L. S. P., and Leitch, I.: The Nutritional Anemias of Man and Animals, Nutrition Abstr. & Rev. 2: 195, 1934. Heath, C. W.: Iron Deficiency in Girls: Chlorosis, M. Clin. North America 21: 389, 1937. Olef, I.: Chlorosis, New England J. Med. 225: 358, 1941.

Anemia, achlorhydia and intestinal disorders appear to be more common in parts of the Scandinavian countries, England, and Scotland and North America, although hereditary influences as well as dietary customs among Nordic peoples may play a role. It is estimated

TABLE 3.—*Estimated Iron Requirements for Growth: Males*

Age, Years	Weight, Kg.	Surface Area, Sq. M.	Total Blood Volume, Cc.	Normal Hemo-globin, Gm. per 100 Cc.	Total Circulating Hemo-globin, Gm.	Annual Gain Circulating Iron, Gm.	Annual Gain Extra-circulating Iron, Gm.	Total Annual Requirement of Iron, Gm.
Birth	3.4	0.226	200	19.46	50.6	0.158	0.037	0.195
1	10.9	0.521	818	11.87	97.1	0.099	0.013	0.112
2	13.4	0.598	1,017	12.42	126.3	0.071	0.009	0.080
3	15.3	0.665	1,184	12.42	147.1	0.062	0.010	0.092
4	17.3	0.749	1,378	12.42	171.1	0.086	0.012	0.098
5	19.6	0.816	1,550	12.08	196.5	0.066	0.013	0.079
6	22.2	0.884	1,680	12.85	215.9	0.068	0.012	0.080
7	24.6	0.948	1,801	13.11	236.1	0.054	0.016	0.070
8	27.9	1.011	1,921	13.11	251.8	0.057	0.015	0.072
9	30.9	1.078	2,048	13.11	268.5	0.134	0.018	0.152
10	34.5	1.168	2,348	13.11	307.8	0.114	0.016	0.130
11	37.6	1.240	2,604	13.11	341.4	0.122	0.015	0.137
12	40.7	1.306	2,878	13.11	377.3	0.168	0.021	0.189
13	44.8	1.403	3,255	13.11	426.7	0.176	0.022	0.198
14	49.3	1.502	3,650	13.11	478.5	0.280	0.034	0.314
15	56.0	1.621	4,134	13.57	561.0	0.290	0.023	0.313
16	60.6	1.706	4,606	14.03	646.2	0.335	0.018	0.353
17	64.3	1.772	5,139	14.49	744.6	0.174	0.009	0.183
18	66.1	1.801	5,493	14.49	795.9	0.143	0.006	0.149
19	67.2	1.813	5,783	14.49	838.0	0.081	0	0.081
20	67.2	1.813	5,947	14.49	861.7	0.071	0	0.071
21	1.813	6,092	14.49	882.7	0.071	0	0
22	1.813	6,092	14.49	882.7	0.071	0	0
23	1.813	6,092	14.49	882.7	0.071	0	0
Total requirement: Birth to 21 years.....								3.148

that iron deficiency is present in at least 16 per cent of the female patients entering the general medical wards of the Boston City Hospital. In an extensive study of individuals belonging to the poorest classes of northeast Scotland, Davidson, Fullerton and Campbell¹⁸ found anemia believed to be iron deficiency in 41 per cent of infants under 2 years, 32 per cent of preschool children,

18. Davidson, L. S. P.; Fullerton, H. W., and Campbell, R. M.: Nutritional Iron Deficiency Anemia, Brit. M. J. 2: 195, 1935.

2 per cent of school children, 16 per cent of adolescent women and 45 per cent of adult women. MacKay¹⁹ reported also an extremely high incidence of iron

TABLE 4.—*Estimated Iron Requirements for Growth of Females, Menstruation and Pregnancy*

Age, Years	Weight, Kg.	Surface Area, Sq. M.	Total Blood Volume, Cc.	"Normal" Hemoglobin, Gm. per 100 Cc.	Total Circulating Hemoglobin, Gm.	Annual Gain Circulating Iron, Gm.	Annual Gain Extra-circulating Iron, Gm.	Loss of Iron by Catamenia, Gm.	Total Annual Requirement or Iron, Gm.
Birth	3.26	0.222	255	19.46	49.6	0.148	0.084	0	0.182
1	10.2	0.500	785	11.87	93.2	0.100	0.012	0	0.112
2	12.5	0.581	988	12.42	122.7	0.079	0.013	0	0.092
3	15.1	0.660	1,175	12.42	145.9	0.068	0.012	0	0.080
4	17.4	0.726	1,136	12.42	165.9	0.077	0.010	0	0.087
5	19.5	0.782	1,486	12.08	188.4	0.091	0.015	0	0.106
6	22.4	0.882	1,676	12.85	215.4	0.065	0.013	0	0.078
7	25.1	0.941	1,788	13.11	234.4	0.053	0.014	0	0.067
8	27.9	1.004	1,908	13.11	250.1	0.088	0.020	0	0.108
9	31.8	1.079	2,104	13.11	275.8	0.103	0.017	0	0.120
10	35.2	1.162	2,336	13.11	306.2	0.143	0.020	0	0.163
11	39.2	1.265	2,657	13.11	348.3	0.142	0.022	0	0.164
12	43.7	1.352	2,974	13.11	389.9	0.171	0.021	0	0.192
13	47.9	1.448	3,359	13.11	440.4	0.131	0.014	0	0.145
14	50.7	1.503	3,652	13.11	478.8	0.151	0.019	0.298	0.468
15	54.5	1.565	3,991	13.11	523.2	0.120	0.006	0.298	0.424
16	55.7	1.578	4,261	13.11	558.6	0.193	0.007	0.298	0.498
17	57.0	1.601	4,643	13.25	615.2	0.135	0.002	0.298	0.435
18	57.4	1.605	4,895	13.38	655.0	0.150	0.004	0.298	0.452
19	58.2	1.621	5,171	13.52	699.1	0.067	0	0.298	0.365
20	1.621	5,317	13.52	718.9	0.060	0	0.298	0.358
21	1.621	5,447	13.52	736.4	0	0	0.298	0.298
22	1.621	5,447	13.52	736.4	0	0	0.298	0.298
23	1.621	5,447	13.52	736.4	0	0	0.298	0.298
24	1.621	5,447	13.52	736.4	0.374*	0	0	0.374
25	1.621	5,447	13.52	736.4	0	0	0.298	0.298
26	1.621	5,447	13.52	736.4				
Total requirement: Birth to 21 years.....									4.006

* Estimated iron requirement for pregnancy.

deficiency anemia in women and infants of the hospital class in London. MacKay²⁰ also presented evidence

19. MacKay, Helen M. M.: Nutritional Anemia in Infancy, J. A. M. A. 98:651 (Feb. 20) 1932 (London Letters); The Hemoglobin Level Among London Mothers of the Hospital Class and Its Probable Bearing on Susceptibility to Infection, Lancet 1:1431, 1935.

20. MacKay, Helen M. M., and Goodfellow, L.: Nutritional Anemia in Infancy: The Influence of Iron Deficiency on Infant Health, Medical Research Council, Special Report Series, No. 157, London, 1931. MacKay (footnote 19, second reference).

indicating that anemia of iron deficiency was associated with a higher incidence of infections. Dietary and hygienic factors will influence the incidence of iron deficiency as well as of other deficiency states in any one locality or at any one time. Cases of iron deficiency, on the other hand, will be present everywhere and at all times as long as pathologic blood loss and other factors interfering with normal physiology of iron exist.

REQUIREMENTS FOR COPPER AND OTHER METALS

The important change in the body when there is a deficiency of iron is an inability to form hemoglobin. There are undoubtedly other widespread changes in the body, examples being the dystrophy of the nails and the atrophy of the pharyngeal mucous membrane in severe chronic iron deficiency, but these are less well understood. Iron forms an essential part of the hemoglobin molecule, which is a protein in which a large molecule, globin, is linked with a smaller iron-containing molecule, hematin. In the absence of available iron, therefore, hemoglobin cannot be formed. Nevertheless there are a number of other substances which in the presence of iron have been shown to influence hemoglobin production. Whipple and his co-workers have been able to arrange certain foodstuffs, among them liver, according to their power of regenerating hemoglobin in dogs rendered chronically anemic by repeated bleeding and maintained on a diet poor in hemoglobin-regenerating factors. Bile pigment, chlorophyll and chlorophyll derivatives are effective when added to small doses of iron in increasing blood regeneration in iron deficiency. Copper has attracted particular attention as an adjuvant to iron therapy, because it has been proved quite definitely that copper is a necessary substance for hemoglobin formation, at least in small animals.²¹ Copper, however, does not form a part of the hemoglobin molecule, and although it is an essential element in human tissues its functions are little understood. Iron deficiency anemia in adult man apparently responds satisfactorily to iron therapy

21. Elvehjem, C. A.: The Biological Significance of Copper and Its Relation to Iron Metabolism, *Physiol. Rev.* 15: 471, 1935. Elvehjem, C. A., and Sherman, W. C.: The Action of Copper in Iron Metabolism, *J. Biol. Chem.* 98: 309, 1932. Frost, D. V.; Potter, V. R.; Elvehjem, C. A., and Hart, E. B.: Iron and Copper versus Liver in Treatment of Hemorrhagic Anemia in Dogs on Milk Diets, *J. Nutrition* 10: 207, 1940.

without supplementary copper feeding. This is not proof that copper isn't needed, but only that supplementary copper therapy is not necessary. The issue is clouded by the fact that most iron preparations used in therapy as well as most foods contain small amounts of copper. A few cases of iron deficiency in man have been treated satisfactorily with copper-free iron. Iron given parenterally in small amounts has been recovered quantitatively in the new-formed hemoglobin.²² Hemoglobin formation in certain cases of childhood anemia has apparently been hastened by supplementing iron therapy with copper,²⁸ although these results have not been conclusive and the thesis that supplementary copper is necessary in the treatment of iron deficiency in childhood has not been supported by others.²⁴

Other metals, such as arsenic, zinc, nickel and manganese in very minute amounts, perhaps have a similar influence to copper.²⁵ Man derives his variegated food from widely different locations, and even much limited diets may contain significant amounts of elements which are present in the body in minute amounts. This is not true of laboratory animals on controlled diets or in the cattle and sheep industry in certain parts of the world. A case in point is the peculiar anemia of cattle and sheep which graze on land the soil of which is poor in certain minerals. This has been investigated by Filmer and Underwood²⁶ in Australia, who found that cobalt is apparently the specific element which is deficient. It is extremely unlikely that specific deficiencies of these minerals other than iron, which are required by the body in minute amounts, will develop in man. The possible exception to this is the case of infants fed on cow's milk exclusively during the first year of life.

22. Heath, C. W.; Strauss, M. B., and Castle, W. B.: Quantitative Aspects of Iron Deficiency in Hypochromic Anemia, *J. Clin. Investigation* **11**: 1293, 1932.

23. Josephs, H. W.: Treatment of Anemia of Infancy with Iron and Copper, *Bull. Johns Hopkins Hosp.* **49**: 246, 1931.

24. Bethel, F. H.; Goldhamer, S. M.; Isaacs, Raphael, and Sturgis, C. C.: The Diagnosis and Treatment of Iron Deficiency Anemia, *J. A. M. A.* **103**: 797 (Sept. 15) 1934. Heath, C. W.: Oral Administration of Iron in Hypochromic Anemia, *Arch. Int. Med.* **51**: 459 (March) 1933.

25. Myers, V. C., and Beard, H. H.: Studies in the Nutritional Anemia of the Rat: II., *J. Biol. Chem.* **94**: 89, 1931.

26. Filmer, J. F.: Enzootic Marasmus of Cattle and Sheep, *Australian Veterinary J.*, **9**: 163, 1933. Filmer, J. F., and Underwood, E. J.: Enzootic Marasmus: Treatment with Limonite Fractions, *ibid.* **10**: 83, 1934. Underwood, E. J., and Filmer, J. F.: Enzootic Marasmus: The Determination of the Biologically Potent Element (Cobalt) in Limonite, *ibid.* **11**: 84, 1935.

RECOMMENDATIONS FOR SATISFYING NUTRITIONAL
REQUIREMENTS FOR IRON AND
OTHER METALS

Iron is widely distributed throughout nature and is probably present in all cells both plant and animal, where it serves an essential use in cellular function.²⁷ The more processed and purified foods consumed by man (e. g. cane sugar, white flour, polished rice) contain less iron as well as other accessory food substances than the cruder products. A diet containing adequate amounts of iron and other minerals should therefore be rich in animal and vegetable cells, should be broadly chosen and should have no excess of highly processed foods. Presumably, if the iron content of the diet is satisfied the content of copper, cobalt, and manganese will be satisfied. Iron deficiency anemia itself, which can and often does arise in spite of adequate iron in the food, is easily treated by the administration of adequate doses of inorganic iron preparations, for example ferrous sulfate 0.3 Gm. (or more) three or four times daily, ferric and ammonium citrate 2 Gm. (or more) three times daily or reduced iron 1 Gm. (or more) three times daily. Smaller doses are given in infancy and childhood. Iron may be properly given as a preventive against the later occurrence of iron deficiency during pregnancy, in infancy and early childhood and in girlhood about the time of puberty.

In table 2 have been given the recommended daily allowances for iron in the diets of children, men and women as recommended by the Committee on Food and Nutrition. These figures are very much greater than the actual physiologic needs of the body for functioning iron, but only a part, usually a very small part, of the iron of the food is absorbed. A well chosen diet, adequate in calories and containing meat, eggs, colored vegetables and whole grain flour, will satisfy or even exceed these requirements. Although such diets would certainly be adequate for all healthy, active men, particularly those in the armed forces, they would be less likely to satisfy the needs of all the civilians, particularly women and children. There is therefore some justification for the proposals to add iron salts to flour for civilian consumption. This is perhaps especially

27. Jones, H. W.: The Distribution of Inorganic Iron in Plant and Animal Tissues, *Biochem. J.* 14: 654, 1920.

justified because of our lack of knowledge of the availability of iron from various foods. Iron in different organic combinations in foods certainly varies in the ease with which it may be liberated by the digestive process for absorption. No satisfactory test has yet been made for determining the availability for man of the iron in different foods. The dipyriddy method has been of some accuracy in determining iron of the food available for rats.²⁸ Probably different individuals will vary greatly in their ability to absorb different kinds of food iron. The accompanying foods, the state of the gastrointestinal tract and the need of the body for iron and other metals will all influence the amount of iron absorbed from a particular food.

The Council on Foods and Nutrition of the American Medical Association has discussed fully the enriching of flour with mineral and vitamin supplements.²⁹ The problem as regards iron is that of the choice of iron preparation, the ease and efficiency of mixing, palatability, the availability of the iron and its possible detrimental effect on other constituents of the enriched flour. Obviously, the questions which this subject raises cannot all be answered even in the near future. It is fairly certain, however, that iron as a simple iron salt added to flour will be more available than the iron in close organic combination in the original flour. There is some indication, on the other hand, that iron salts mixed with other substances before feeding are less available for absorption than when fed alone.³⁰ There has also been demonstrated a relationship between the utilization of iron and the amounts of calcium and phosphorus in the diet³¹ and other interrelationships will undoubtedly be established. At the present time it would appear that if whole grain flours were widely used, and the advantages of a widely chosen and adequate diet were promulgated, nutritional requirements for iron and other minerals (with pos-

28. Elvehjem, C. A.; Hart, E. B., and Sherman, W. C.: The Availability of Iron from Different Sources for Hemoglobin Formation, *J. Biol. Chem.* **103**: 61, 1933.

29. Nutritionally Improved or Enriched Flour and Bread, *J. A. M. A.* **110**: 2849 (June 28) 1941.

30. Heath, C. W.; Minot, G. R.; Pohle, F. J., and Alsted, G.: The Influence of Mucin on the Absorption of Iron in Hypochromic Anemia, *Am. J. M. Sc.* **195**: 281 (March) 1938.

31. Anderson, H. D.; McDonough, K. B., and Elvehjem, C. A.: Relation of Dietary Calcium Phosphorus Ratio to Iron Assimilation, *J. Lab. & Clin. Med.* **25**: 464, 1940.

sible exceptions of calcium and phosphorus) would be adequately supplied. On the other hand, there is no definite indication that harm would result from the addition of small amounts of iron salts to flour. There is no more useful field in nutritional research at the present time than the exploration of the adequacy and inadequacy of different foods and enriched foods in supplying substances necessary to the health of man.

CHAPTER VIII

IODINE IN NUTRITION

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In the struggle for survival in this world conflict, in which both physical and emotional demands on the body's resources are rapidly mounting, the problems of nutrition assume an even greater significance. And thus iodine, a nutritional necessity, essential in the normal regulation of the energy output of the human body, comes to take its place in any all inclusive war effort.

DISTRIBUTION OF IODINE AND GOITER

Iodine is widely distributed throughout all nature. It occurs in many forms, both organic and inorganic. It is found in nearly all living things as well as in the air, water, soil and rocks. Not the sea, as is popularly believed, but the earth's crust is the major storehouse of iodine.¹

Iodine is not uniformly distributed but varies with the local geologic conditions of the soil and water. Inversely related to the distribution of iodine is the incidence of endemic goiter. The highest incidence of goiter is found among the Alps, Pyrenees and Himalayas, the Thames Valley in England, certain inhabited districts of New Zealand, the region of the Great Lakes and the Pacific Northwest.²

Throughout the United States there are similarly varying degrees of iodine deficiency. A low occurrence of iodine together with a high incidence of goiter are especially prominent in the Central Plain of North America, in contrast to the low incidence of goiter on the sea coasts, where large amounts of high iodine containing sea foods are consumed. On the other hand, the district of Salt Lake City has a high incidence of goiter even though the water of Great Salt Lake has a higher

Aided by a grant from the Comly Fund for Research of the Ohio State University.

1. Orr and Leitch,^a McClendon,^a von Fellenberg.⁶⁰

2. McClendon, J. F.: Iodine and the Incidence of Goiter, Minneapolis, University of Minnesota Press, 1939.

iodine concentration than the ocean. However, neither vegetation nor fish for human consumption comes from the nearly lifeless waters of the Great Salt Lake.²

The incidence of goiter can be correlated with the iodine intake of a given region. This in turn is largely dependent on the soil iodine. Intake iodine is derived essentially from the food and to a lesser degree from unsupplemented salt or from water.³ About 14 micrograms daily was formerly said to represent the difference in iodine intake between goitrous and nongoitrous regions.⁴ However, even this low regional difference in iodine consumption becomes less pronounced as the interstate transportation of foods, drinks, vegetables, fruits and fertilizers increases.

The amount of iodine in the local drinking water may be regarded as a measure of the iodine content of the soil and, consequently, of the fruits, grains, grasses and vegetables grown in the region. It is not, however, important as a source of nutritional iodine save in unusual circumstances.¹ McClendon has divided the United States into sections according to the iodine content of the waters. In a section extending from Oregon to the western part of Maine, and in another from Nevada to the western part of Virginia, the water iodine is low and the incidence of goiter high.² Likewise the Michigan studies reveal that the incidence of goiter in a given locality is inversely proportional to the amount of iodine found in its waters.⁵

The food iodine is the most important factor determining the goiter incidence in a given region. Japan presents an outstanding example of a goiter free area. Yet Formosa, which, like Japan, is geologically low in iodine, has a high incidence of goiter. The absence of goiter in Japan is a consequence of the extensive importation and consumption of seaweed, which is rich in iodine.²

In South Carolina, where the incidence of goiter is low, the amount of iodine in the vegetables is considerably higher than in the more goitrous Northern and Western states.⁶ Yet the cotton and tobacco grow-

3. Orr, J. B., and Leitch, I.: Iodine in Nutrition, Medical Research Council, Special Series Report No. 123, London, 1929.

4. Hercus, C. E., and Roberts, K. C.: The Iodine Content of Foods, Manures and Animal Products in Relation to the Prophylaxis of Endemic Goiter in New Zealand, *J. Hyg.* **26**: 49, 1927.

5. Reports cited in footnotes 63 and 66.

6. Weston, W.: Foods in the Solution of the Goiter Problem, *South. M. J.* **23**: 479, 1930.

ing South as a whole, comprising a great part of the goiter free United States,⁷ fails to produce sufficient food and feed crops for its own needs.⁸ Thus, most of the canned foods and other food products in the United States come from sections of the country poor in iodine.⁷

The regional incidence of goiter is also correlated with the milk iodine of the area.⁹ This follows, since the iodine content of the soil and vegetation determines the iodine intake of the lactating mammal.¹⁰ Consequently, the milk iodine depends on the soil of the locality from which it is obtained, provided supplemental iodine is not being consumed.¹¹ This is also true of eggs and other food products.¹²

In the Chinese province of Yunnan there is a high incidence of goiter and considerable cretinism. Men and women working on the Burma Road show an incidence of thyroid enlargement as high as 80 per cent, with an average well over 50 per cent. Residence in a Yunnan goitrous district for six months appears sufficient to produce thyroid enlargement in susceptible individuals. Iodine deficiency in the provincial salt and vegetation appears responsible. As the result of military occupation by the Japanese, the hinterland of China is now cut off from its former coastal supply of high iodine-containing salt. Consequently large areas of free China must now depend on Yunnan salt, which is deficient in iodine.¹³

IODINE AND THE NORMAL THYROID GLAND

The human thyroid gland is a principal storehouse for iodine. Weighing ordinarily about 25 Gm. and containing about 10 mg. of iodine, it normally maintains an iodine concentration of around 40 mg. per hundred grams. It was shown long ago by Marine and Lenhart that, when this concentration falls below 10 mg. per

7. McClendon.² Olesen.⁸

8. Olesen, R.: Endemic Goiter, U. S. Pub. Health Bulletin, **192**: 27, 1929. Opportunity or Calamity, editorial, Food Industries, November 1931, pp. 467-469.

9. Orr and Leitch.³ Shore and Andrew.¹²

10. Meyer, J. H.: The Iodine Content of Milk, Thesis for M.S., Dept. Surg. Res., Ohio State University, 1940.

11. Shore and Andrew.¹² Meyer.¹⁰

12. Shore, R. A., and Andrew, R. L.: Goiter in School Children: The Incidence of Goiter in School Children in Relation to the Amount of Iodine in Soil and Water in Certain Districts of the North Island in New Zealand, Dept. Health & Sc. & Ind. Research, Wellington, 1929, Bull. Hyg. **5**: 94, 2, 1930.

13. Robertson, R. Cecil: The Problem of Endemic Goiter in Yunnan Province, J. Clin. Endocrinol. **1**: 285, 1941.

hundred grams, hyperplasia ensues and goiter may consequently develop.¹⁴

No other organ of the body has the power of iodine concentration possessed by the thyroid gland. The whole blood iodine averages less than 1 part in 25 million, while the thyroid gland normally contains approximately 1 part in 25 hundred. This indicates that the thyroid gland can concentrate the iodine it obtains from the blood by a factor of at least 10,000.

Within the colloid in the alveoli of the thyroid gland, iodine is stored in the form of the amino acids diiodotyrosine and thyroxin containing respectively 59 and 65 per cent iodine. King suggests that the thyroid hormone has undergone a process of evolutionary development in complexity, from a simpler physiologically active iodine compound produced in the tissues.¹⁵

The accepted facts of thyroid physiology indicate that iodine is selectively absorbed by the active thyroid gland. Furthermore, in some measure the glandular function is regulated by its iodine content. Studies with radioactive iodine have shown that iodine is quickly brought to the gland by the blood stream and rapidly converted by the thyroid cells into organic compounds; moreover, that within a matter of a few hours these organic iodine compounds may return to the circulation.¹⁶

The total thyroid iodine content varies directly with the weight of the gland, while the relative iodine content is inversely proportional to its weight.¹⁵ This inverse relationship between the size of the thyroid and its iodine concentration was noted as early as 1896 by Baumann¹⁷ and was later confirmed by Marine and

14. Marine, David, and Lenhart, C. H.: Further Observations of the Relation of Iodine to the Structure of the Thyroid Gland in the Sheep, Dog, Hog and Ox, *Arch. Int. Med.* **3**: 66 (Feb.) 1909.

15. King, J. D.: The Iodine Content of the Normal Thyroid Gland Correlated with Its Histology and the Iodine Content of Other Normal Body Tissues in Central Ohio, Dissertation for Ph.D., Dept. Surg. Res., Ohio State University, 1940.

16. Perlman, I.; Chaikoff, I. D., and Morton, M. E.: Radioactive Iodine as an Indicator of the Metabolism of Iodine; I. The Turnover of Iodine in the Tissues of the Normal Animal with Particular Reference to the Thyroid, *J. Biol. Chem.* **139**: 433 (May) 1941. Perlman, I.; Morton, M. E., and Chaikoff, I. L.: Radioactive Iodine as an Indicator of the Metabolism of Iodine: II. The Rates of Formation of Thyroxin and Diiodotyrosine by the Intact Normal Thyroid Gland, *ibid.* **139**: 449 (May) 1941. Curtis, G. M., and Davison, R. A.: Unpublished data.

17. Baumann, E.: Ueber den Jodgehalt der Schilddrüsen von Menschen und Thieren, *Ztschr. f. physiol. Chem.* **22**: 1, 1896.

Lenhart in 1909.¹⁴ The thyroid iodine content varies inversely with the incidence of nodule formation, the percentage of epithelial proliferation, the height of the follicular epithelium, the incidence of lymphocytic infiltration and the occurrence of degenerative changes.¹⁵

Iodine intake is the principal factor which determines the iodine content of the thyroid and overshadows other differences due to species, age or sex. Small differences in the supply of iodine are reflected in the iodine content of the gland.³ The thyroid fixes a relatively higher percentage of iodine from smaller doses of administered iodide than from larger.¹⁸

Since iodine intake is so largely dependent on the soil and consequently on plant iodine, the gland concentration varies with the geographic distribution of iodine. Thus, in nongoitrous Texas the fat free thyroid contains 6 mg. of iodine per gram, whereas in goitrous North Dakota it contains only 3.2 mg. per gram.¹⁹

King found the total thyroid iodine higher from May through October than from November through April, although the gland concentration remained fairly constant.¹⁶ The iodine content of the ruminant thyroid was found to be maximum in late summer and early fall and at a minimum in winter and early spring.²⁰ This variation in thyroid iodine may be attributed to fluctuation in the amount of iodine available from the pastures.²¹ Perhaps more fundamental than the season per se is variation in the foodstuffs available during each season.²² Orr and Leitch analyzed various plants grown in Scottish pastures and collected during different months of the grazing seasons. They demonstrated an increase in the autumn iodine content.⁸

Age as well as sex differences in thyroid iodine have also been reported.⁸

18. Leblond, C. P., and Sue, P.: Iodine Fixation in the Thyroid as Influenced by the Hypophysis and Other Factors, *Am. J. Physiol.* **134**: 549 (Oct.) 1941.

19. Fenger, F.; Andrew, R. H., and Vollertson, J. J.: Geographic Location and the Iodine Content of the Thyroid Gland, *J. Am. Chem. Soc.* **53**: 237, 1931.

20. Seidell, A., and Fenger, F.: Seasonal Variation in the Iodine Content of the Thyroid Gland, *J. Biol. Chem.* **13**: 517, 1913. Kendall, E. C., and Simonsen, D. G.: Seasonal Variations in the Iodine and Thyroxin Content of the Thyroid Gland, *ibid.* **80**: 357, 1928.

21. Matthews, N. L.; Curtis, G. M., and Meyer, J. H.: The Effect of Increased Iodine Feeding on the Iodine Content of Cow's Milk, *J. Dairy Res.* **10**: 395, 1939. Meyer, J. H.; Matthews, N. L., and Curtis, G. M.: A Study of the Effects of Increased Iodine Feeding to a Herd of Sixty Dairy Cows, *Ohio J. Sc.* **40**: 9, 1940. Orr and Leitch.⁸

22. Shore and Andrew.¹⁹ Matthews, Curtis and Meyer.²¹ Meyer, Matthews and Curtis.²²

IODINE AND THE PATHOLOGIC THYROID GLAND

Endemic goiter and its sequelae are fundamentally a result of iodine deficiency.²³ The ultimate cause of endemic goiter, however, is not clear. The immediate cause is a deficiency of iodine, necessary in the production of the high iodine containing thyroid hormone. This deficiency may be absolute, as in areas of subnormal iodine intake, or it may be relative, subsequent to various demands on the body which increase the needs for thyroid secretion.²⁴ Such factors include puberty, pregnancy, lactation, the incidence of infectious diseases, ingestion of toxic substances and high calcium intake, as well as those conditions which interfere with the gastrointestinal absorption of iodine.

The microscopic changes in the thyroid closely parallel the chemical findings.¹⁵ Baumann and Roos²⁵ and also Oswald²⁶ were the first to observe that, if iodine is withheld, compensatory hypertrophy of the thyroid occurs. They noted that the iodine content of the thyroid is proportional to the amount of colloid present and that in colloid goiter the concentration of iodine is definitely below that found in the normal gland.

When normal or goitrous thyroid glands obtained from goitrous regions are compared with other normal or goitrous glands, it is found that the glands from the goitrous regions are the largest and have the highest incidence of nodule formation, the smallest follicular size and the lowest iodine content.¹⁵

If iodine is administered to a person with a normal thyroid gland or with a colloid goiter there is a subsequent increase in the iodine content of the gland, with no notable change in its structure and with no hyperplasia of the remaining lobe after single lobectomy. If iodine is withheld, however, the iodine content of the gland gradually decreases, and hyperplasia will ensue if one lobe is removed.¹⁴

Remington and his associates have shown that it is possible to produce enlarged and hyperplastic thyroid

23. King.¹⁵ Marine.⁶⁰ Elmer.²⁴

24. Elmer, A. W.: *Iodine Metabolism and Thyroid Function*, London, Oxford University Press, 1938.

25. Baumann, E., and Roos, E.: *Ueber das normale Vorkommen des Jods in Thierkörper: II. Mitt., Ztschr. f. physiol. Chem.* 21:481, 1896.

26. Oswald, A.: *Ueber den Jodgehalt der Schilddrüsen, Ztschr. f. physiol. Chem.* 23:265, 1897.

glands in young rats fed for five weeks on a diet extremely low in iodine.²⁷ The addition of iodide to the diet prevented the development of goiter; nevertheless, increased iodine intake by newborn rats during the first four weeks of life did not permit sufficient storage of iodine to prevent the development of goiter when iodine was later withdrawn. Varying the calcium content of the ration or its calcium-phosphorus ratio or the presence or absence of vitamin D did not significantly affect the degree of goiter produced.²⁷

The blood iodine is increased during pregnancy.²⁸ There is also an increased loss of iodine in the urine.²⁹ Thyroid hyperplasia may be demonstrated in from 70 to 80 per cent of pregnant women²⁴ and may also occur during lactation, since considerable iodine is lost in the milk.²⁴ It has been noted that feeding iodine to pregnant animals prevents microscopic pathologic changes in the thyroid.³⁰

IODINE AND THE EXTRATHYROID TISSUES

The total iodine content of the human body is variable and depends on divers factors. A normal man weighing 70 Kg. may be estimated reasonably to contain about 50 mg. of iodine, which is equivalent to about 1 part in 1,400,000 of body substance. Iodine thus forms less than 0.00008 of 1 per cent of the body weight. Every cell in the body is said to contain some iodine;³¹ however, of the total body iodine, about one half can be assigned to the muscles, one fifth to the thyroid, one tenth to the skin and one seventeenth to the bones.³²

27. Remington, R. R., and Levine, H.: Studies on the Relation of Diet to Goiter: III. Further Observations on a Goitrogenic Diet, *J. Nutrition* **11**: 343, 1936.

28. Curtis, G. M., and Fertman, M. B.: The Blood Iodine in Health and Disease, unpublished data.

29. Enright, Lena; Cole, Versa V., and Hitchcock, F. A.: Basal Metabolism and Iodine Excretion During Pregnancy, *Am. J. Physiol.* **113**: 221 (Sept.) 1935. Puppel, I. D., and Curtis, G. M.: Iodine Balance in Exophthalmic Goiter, *Arch. Path.* **26**: 1093 (Dec.) 1938; The Iodine Balance in Nodular Goiter, *J. Clin. Investigation* **17**: 729 (Nov.) 1938.

30. Schmelling, J. W.: Over de normale en vergroote Schildklier geduren de embryonale ontwikkeling, bij den pasgeborene en pasgeborene en bij het jonge Kind in Nederland, Dissertation, Utrecht, 1934.

31. Justus, J.: Ueber den physiologischen Jodgehalt der Zelle, *Virchows Arch. f. path. Anat.* **170**: 500, 1902.

32. Sturm, A., and Buchholz, B.: Beiträge zur Kenntnis des Jodstoffwechsels: Jodverteilung im menschlichen und tierischen Organismus in ihrer Beziehung zur Schilddrüse, *Deutsches Arch. f. klin. Med.* **161**: 227, 1928.

Several investigators maintain that the iodine concentration of the endocrine glands, exclusive of the thyroid and parathyroids, exceeds that of the nonendocrine tissues.³³ King, investigating mammalian tissue iodine,¹⁵ and Libecap, determining the iodine content of normal human tissues,³⁴ were unable to confirm this relatively high iodine content attributed to the nonthyroid endocrines. Moreover, they both found that the iodine content of the pituitary, as well as of the central nervous system, was unusually low.

The importance of the liver in the physiology of iodine is emphasized by Elmer.²⁴ This is further supported by the consistently high iodine content found in the bile.³⁵ With the exception of the thyroid gland and the hair, bile contains the highest iodine concentration in the human body.³⁴

Von Fellenberg found that the lungs retain more injected iodine than other organs; however, they may also lose it more rapidly. Since the administration of iodide did not increase the amount of iodine in the expired air, he concluded that the lungs lose iodine in some other manner.³⁶ Ariel and his co-workers³⁷ and Lein,³⁸ independently using radioactive iodine, found that, next to the thyroid gland, the lungs collect most of the iodine injected. Lein was unable to correlate the large quantity of iodine held in the lungs with the iodine expired in the air.

IODINE AND THE BODY FLUIDS

Human blood normally contains a fairly constant concentration of iodine. Fractionation studies reveal that about a fourth of this appears to form part of the

33. Bourcet, M. P.: Sur l'iode normal de l'organisme et son élimination, *Compt. rend. Acad. d. sc.* **131**:392, 1900. Maurer, E.; Ducrue, H., and Palasoff, W.: Untersuchungen über das Vorkommen von Jod im menschlichen und tierischen Organismus, München. med. Wchnschr. **74**:271, 1927. Maurer, E., und Ducrue, H.: Zur Kenntnis des Jods als biogenes Element.; der Jodgehalt im normalen tierischen Organismus, *Biochem. Ztschr.* **217**:227, 1930. Sturm and Buchholz.³² von Fellenberg.³⁶

34. Libecap, I. L.: The Iodine Content of Normal Human Tissues, Thesis for M. M. Sc., Department of Surgical Research, Ohio State University, 1942.

35. King.¹⁵ Libecap.³⁴

36. von Fellenberg, T.: Versuche über die Jodspeicherung in den einzelnen Organen, *Biochem. Ztschr.* **174**:355, 1926.

37. Ariel, Irving; Bale, W. F.; Downing, Vincent; Hodge, H. C.; Mann, Walter; Van Voorhis, Stanley; Warren, S. L., and Wilson, Helen J.: The Distribution of Radioactive Isotopes of Iodine in Normal Rabbits, *Am. J. Physiol.* **132**:346 (March) 1941.

38. Lein, A.: Studies on the Rate of Certain Iodine Reactions in the Thyroid Gland, unpublished data.

circulating thyroid hormone.³⁹ The other three fourths, consequently, would represent the iodine of nutrition together with products of the breakdown of the high iodine containing thyroid hormone.

Various values, ranging from 3 to 20 micrograms per hundred cubic centimeters, have been ascribed by different investigators to the normal blood iodine level.⁴⁰ These vary with the method of iodine determination, the geographic area and divers other factors. The average blood iodine of 29 normal individuals in central Ohio was found to be 4.2 plus or minus 1.2 micrograms per hundred cubic centimeters.²⁸ The blood iodine is significantly increased during pregnancy, during parturition, in unmedicated toxic nodular as well as in exophthalmic goiter (chart 3) and in certain non-thyroid diseases.⁴¹ The higher blood iodine observed in certain patients with treated toxic nodular or with exophthalmic goiter may be due to the iodine medication of these patients,⁴² since the administration of iodine in all forms thus investigated increases the circulating blood iodine ⁴³ (chart 1).

In hypothyroidism the average total blood iodine may not differ as significantly as might be expected from the normal.²⁸ However, the acetone insoluble fraction, which presumably contains the circulating thyroid hormone, has an average value of about one-half normal and a range which barely overlaps the lower normal.³⁹

Blood iodine levels vary, as does the concentration of the thyroid iodine; however, the range is narrower.²⁴ Some find a variation of the blood iodine with age,⁴⁴ others maintain that there is a seasonal variation,⁴⁵

39. Davison, R. A., and Curtis, G. M.: Acetone Fractionation of Blood and Urinary Iodine, *Proc. Soc. Exper. Biol. & Med.* **41**: 637, 1939. Davison, R. A.; Zollinger, R. W., and Curtis, G. M.: The Fractionation of the Blood Iodine: I. Findings in Patients with Normal Thyroid Function and with Hypothyroidism, *J. Lab. & Clin. Med.* **27**: 643, 1942.

40. Davis, C. B.; Curtis, G. M., and Cole, V. V.: The Normal Iodine Content of Human Blood, *J. Lab. & Clin. Med.* **19**: 818, 1934.

41. Curtis, G. M.; Cole, V. V., and Phillips, F. J.: Blood Iodine in Thyroid Disease, *West. J. Surg.* **42**: 435, 1934.

42. Curtis, G. M.: The Iodine Relationships of Thyroid Disease, *Surg., Gynec. & Obst.* **62**: 365, 1936.

43. Curtis, G. M.: Iodine Metabolism in Toxic Goiter, *J. Med.* **15**: 148, 1934. Orr and Leitch.³ Elmer.²⁴ Salter.⁵⁰

44. Bürger, M., and Möbius, W.: Der Jod und Cholesteringehalt des Blutes in seinen Beziehungen zur essentiellen Hypertonie, *Klin. Wchnschr.* **18**: 1349, 1934.

45. Veil, W. H., and Sturm, A.: Beiträge zur Kenntnis des Jodstoffwechsels, *Deutsches Arch. f. klin. Med.* **147**: 166, 1925. Kato, S.: Ueber die Verteilung des in der Körper eingeführten Jods auf verschiedene Organe, *Tohoku J. Exper. Med.* **29**: 442, 1936. Ito,⁴⁰

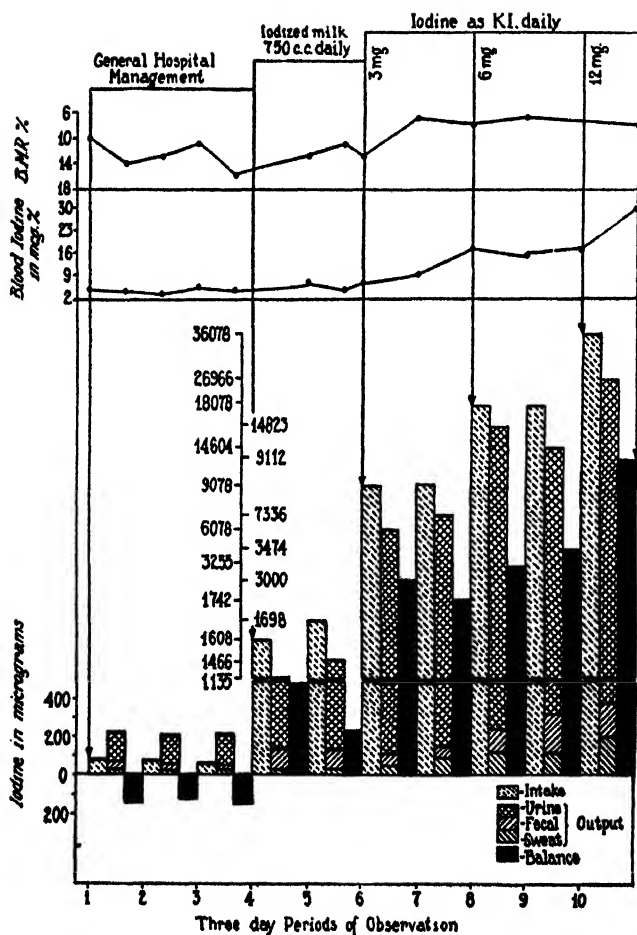


Chart 1.—A thirty day iodine balance of a normal person (J. R., a man aged 56, Oct. 10-Nov. 13, 1936). On the original low iodine intake the balance is negative and the principal iodine loss is in the urine. Iodine storage occurs after giving milk with an increased iodine content obtained from a dairy herd receiving supplemental iodine and further increases when small amounts of iodide are administered daily. Note the consequent rise in the blood iodine. Reproduced from a chart that appeared originally in the *Annals of Surgery*, October 1938, p. 579.

while some note sex differences in the blood iodine level.⁴⁶ We were unable to substantiate either a significant sex difference or any seasonal difference in a study of hundreds of patients with various diseases.²⁸

In certain diseases either the blood iodine or the basal metabolic rate is independently affected; in others the two follow a similar course. We have found the blood iodine significantly correlated with the basal meta-

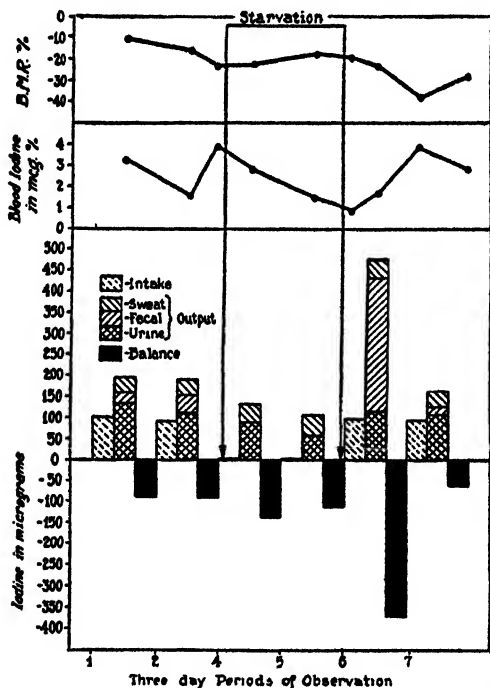


Chart 2.—Effect of starvation on the normal iodine balance (R. B., a youth aged 19; normal; constant regimen and starvation; Nov. 17-Dec. 8, 1936). Note the negative balance on the original low iodine intake. Loss of iodine in the urine and sweat continues during starvation. Reproduced from a chart that appeared originally in the *Annals of Surgery*, October 1938, p. 580.

bolic rate in 70 patients with toxic diffuse goiter, in 29 with toxic nodular goiter and in 80 with nontoxic nodular goiter ²⁸ (chart 3). Möbius and Nolte like-

46. Ito, Nakao: Iodine Metabolism of Patients Suffering Endemic Goiter in Jehol. I. Blood Iodine Content of a Healthy Person, *J. Orient. Med.* 28: 529, 1938. Baumann, E. J., and Metzger, N.: On the Amount of Iodine in the Blood, *J. Biol. Chem.* 121: 231, 1937.

wise have noted correlation between the basal metabolic rate and increased blood iodine.⁴⁷

Thyroidectomy, either for thyroid disease or experimentally, exerts an important effect on the blood iodine. Immediately following total thyroidectomy there ensues a transient increase in the blood iodine, which persists for about thirty-six hours. After varying periods following total thyroidectomy the blood iodine decreases to about one-third normal.⁴⁸

Under maintained basal conditions the normal adult excretes a surprisingly constant amount of iodine in the urine⁴⁹ (chart 1). The urinary iodine varies geographically. It is higher in sea coast regions than in those inland²⁴ and is higher in nongoitrous than in goitrous regions. In five nongoitrous regions from 72 to 343 micrograms a day, averaging 165 micrograms, was excreted; in contrast to a range of from 27 to 64 a day, averaging 42 micrograms, in five goitrous regions.⁴⁹ The average amount of urinary iodine excreted during twenty-four hours by normal adults in central Ohio, a moderately goitrous region, is 51 micrograms.⁵⁰

Several factors increase the loss of iodine in the urine, such as hyperthyroidism⁵¹ (chart 3), menstruation,⁵² pregnancy,²⁹ surgery⁵³ and the administration of iodine in nearly all forms⁵⁴ (chart 1). Milk with an increased iodine content, obtained from dairy herds fed supplemental iodine and given to patients with varying types of thyroid disease as well as to other hospital patients, consistently increased the urinary output of iodine. The patients were thus maintained in

47. Möbius, W., and Nolte, F. A.: Verhalten von Grundumsatz und Blutjod bei Thyreotoxikosen, *Ztschr. f. klin. Med.* **128**: 174, 1935.

48. Curtis, G. M.; Barron, L. E., and Phillips, F. J.: The Blood Iodine After Total Thyroidectomy in Man, *J. Lab. & Clin. Med.* **20**: 813, 1935.

49. Curtis, G. M.; Puppel, I. D.; Cole, V. V., and Matthews, N. L.: The Normal Urinary Iodine of Man, *J. Lab. & Clin. Med.* **22**: 1014, 1937.

50. Curtis, G. M., and Puppel, I. D.: Urinary Iodine in Thyroid Disease, *West. J. Surg., Obst. & Gynec.* **45**: 417, 1937. Curtis, Puppel, Cole and Matthews.⁴⁹

51. Curtis, G. M., and Puppel, I. D.: Increased Urinary Excretion of Iodine in Hyperthyroidism, *Arch. Int. Med.* **60**: 498 (Sept.) 1937.

52. Cole, V. V., and Curtis, G. M.: Cyclic Variations in Urinary Excretion of Iodine in Women, *Proc. Soc. Exper. Biol. & Med.* **31**: 29, 1933.

53. James, A. G.: The Postoperative Loss of Iodine in the Urine, Thesis for M.A. degree, Department of Surgical Research, Ohio State University, 1937. Curtis and Puppel.⁵⁰

54. Curtis, Puppel, Cole and Matthews.⁴⁹ Curtis and Puppel, footnotes 50 and 55.

a positive iodine balance ⁵⁵ (chart 1). On the other hand, fasting decreases the urinary excretion of iodine ⁵⁵ (chart 2). However, the decrease is less if the fasting is preceded by an iodine rich diet. ⁵⁶

Iodine has been demonstrated in lymph, ⁵⁷ cerebrospinal fluid, ⁵⁸ perspiration ⁵⁹ (chart 3), chyle, ascitic fluid, pleural exudates and milk. In milk it plays an important role in supplying needed iodine to the grow-

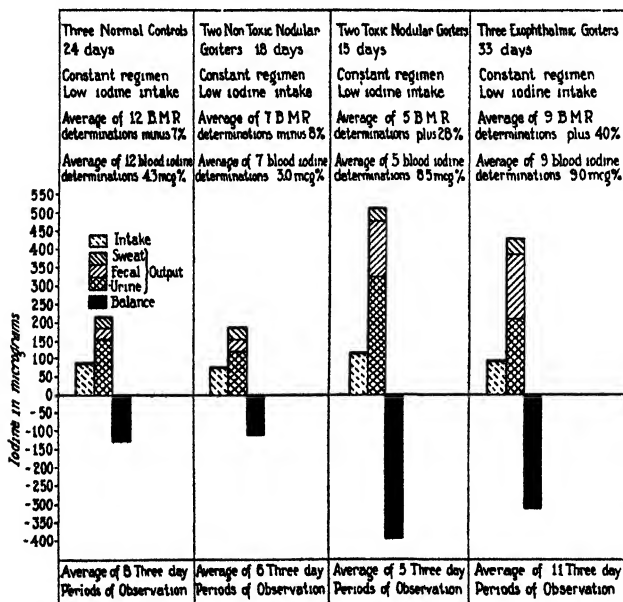


Chart 3.—A comparison of the average iodine balance of three normal persons with that of 4 patients with nodular goiter and 3 with exophthalmic goiter. All were maintained on a low iodine intake. Reproduced from a chart that appeared originally in the Journal of Clinical Investigation, November 1938, p. 734.

55. Curtis, G. M., and Puppel, I. D.: The Iodine Metabolism in Thyroid Disease, Tr. Third International Goiter Conference, Washington, D. C., 1938, p. 367; The Iodine Metabolism in Exophthalmic Goiter, Ann. Surg. **108**: 574 (Oct.) 1938.

56. Salter, W. T.: The Endocrine Function of Iodine, Cambridge, Mass., Harvard University Press, 1940.

57. Schneider, E., and Widmann, E.: Klinische und experimentelle Untersuchungen zum Problem des Kropfes und der Basedowschen Krankheit: 1. Untersuchungen zur Frage des Blutjodgehaltes, Deutsche Ztschr. f. Chir. **231**: 305, 1931.

58. Klassen, K. P.; Bierbaum, R. L., and Curtis, G. M.: The Comparative Iodine Content of the Blood and Cerebrospinal Fluid, J. Lab. & Clin. Med. **25**: 383, 1940.

59. Cole, Versa V.; Curtis, G. M., and Bone, Mary L.: The Iodine Content of Hospital Foods, J. Am. Dietet. A. **10**: 200 (Sept.) 1934. Cole, Versa V., and Curtis, G. M.: Human Iodine Balance, J. Nutrition **10**: 493 (Nov.) 1935.

ing infant, with a resultant depletion of the mother.¹⁰ If iodine feeding is essential to health, it is even more necessary to the lactating as well as to the pregnant mammal. The loss of iodine in the milk results in depletion of the mother's iodine reserve with an ensuing negative iodine balance. This loss should be compensated by a sufficiently large, previously built up iodine reserve or by an increased intake. Otherwise iodine deficiency goiter may develop.⁶⁰ Administration of iodine to mammals increases the milk iodine.⁶¹

GOITER PROPHYLAXIS BY IODINE

"The results of iodine treatment of goiter have been so successful and so well recognized by the lay public that they constitute a chapter unique in the history of nutrition."⁶²

Fortunate was the empiricism which led the ancients to use burnt sponge or seaweed in the treatment of goiter. Iodine was then unknown. It was not until the year 1811 that iodine was accidentally discovered by Courtois as a by-product resulting from the use of seaweed in preparing war materials for Napoleon. Within a few years Sir Humphry Davy had isolated iodine from sponges, seaweed and other forms of marine life. Thence followed a fruitful century of clinical investigation, extending from Straub of Berne to Plummer of Rochester, and of fundamental experimental researches dating from Boussingault of Paris through Chatin, Baumann, Kendall, Marine, von Fellenberg and others to Harington of London.

Today iodine prophylaxis against goiter is most widely recognized, while iodized salt is used throughout the entire United States, even on Nantucket Island and in the Philippines.⁶³ The extensive and increasing popularity of the use of iodized salt obtained an original impetus from the experiments of Marine and his co-workers in Akron, Ohio.

60. Marine, David: Studies on the Etiology of Goiter, Including Graves' Disease, *Ann. Int. Med.* 4:423, 1930; The Importance of Relative Iodine Deficiencies in Certain Forms of Goiter, *J. Am. Dietet. A.* 9:1, 1933. Elmer.⁶⁴

61. Scharrer, K., and Schwaibold, J.: Zur Kenntnis des Jods als biogenes Element; Ueber den Chemismus des tierischen Jodstoffwechsels, *Biochem. Ztschr.* 180:307, 334, 1927. Scharrer, K., and Schropp, W.: Zur Kenntnis des Jods als biogenes Element: XXII. Fütterungsversuch mit steigenden Jodgaben an Milchkühen, *ibid.* 213:18, 1929. von Fellenberg,⁶⁵ Meyer.¹⁰ Matthews, Curtis and Meyer.²¹ Meyer, Matthews and Curtis.²¹

62. White House Conference on Child Health and Protection Nutrition: Iodine in Nutrition, Section 1, p. 260, Medical Service, 1932.

63. Report of the Initial Meeting of the Study Committee on Endemic Goiter of the American Public Health Association, Detroit, June 14-15, 1941.

Marine's significant studies on the prevention of goiter were made on a large group of schoolgirls. Approximately one half voluntarily received sodium iodide daily in a 0.2 Gm. dose distributed over a period of two weeks each spring and fall. The results of two and one-half years of observation showed that of the girls who had no goiter at the beginning of the test 0.2 per cent of the 2,190 receiving iodine developed enlarged thyroid glands, while 21.5 per cent of the 2,305 who did not receive supplemental iodine developed goiter. Of the girls with an initial thyroid enlargement 65.4 per cent of 1,182 who received iodine showed a reduction in the size of the thyroid gland at the end of the year, in contrast to the 13.8 per cent of the untreated 1,048 who showed some diminution in the size of the goiter.⁶⁴ In this same study Marine and Kimball point out that goiter is most apt to develop during fetal life, puberty or pregnancy.

The character and results of the Ohio demonstration stimulated other similar efforts throughout the world, particularly in Switzerland, Austria and Germany. Iodine prophylaxis in Switzerland brought with it the steady decline year by year of cretinism, such an important economic factor to the Swiss. The institution of iodized salt in the canton of Appenzell in 1922 reduced enlarged thyroid glands in newborn infants from an incidence of 50 per cent to almost nothing. The consumption of iodized salt in the canton of Vaud, as a result of the efforts of the Swiss goiter commission, brought about in fifteen years a decline of goiter incidence from 77 to 21 per cent.⁶⁵

The Iodized Salt Committee of the Michigan State Medical Society was organized in 1922. Common salt, iodized to contain 0.02 per cent of sodium iodide, was subsequently introduced by that committee in cooperation with the state board of health in 1924. The results of its consumption were convincing. From 1924 to 1935 there ensued a 75 to 90 per cent decrease in the incidence of goiter in those counties using the iodized salt.⁶⁶ The incidence of goiter operations in seven large

64. Marine, David, and Kimball, O. P.: Prevention of Goiter in Man, *J. A. M. A.* 77:1068 (Oct. 1) 1921.

65. Eggenberger, H.: Kropf und Kretinismus, *Hirsch Handbuch der Inneren Sekretion* 3, numbers 3 and 4, Leipzig, Kabitsch, 1927.

66. First Official Report of the Goiter Survey of Michigan: Study of the Effect of the Use of Iodized Salt on the Incidence of Goiter, *J. Michigan M. Soc.* 36: 647, 1937.

hospitals in southern Michigan dropped from 1,452 in 1927 to 591 in 1933. There was a 60 per cent decrease in goiter operations as compared with a 17 per cent all operation decrease during the corresponding depression years.⁶⁷

Iodine supplementally administered in the form of iodized salt, when thus extensively used, has repeatedly proved beneficial in the prevention of goiter. Its curative effect, however, depends on the character of the goiter as well as on the patient's age at the time of institution of iodine treatment. While it is of value to patients with colloid goiters,³ little beneficial change may be expected in older patients with goiters of long standing in which there are extensive pathologic alterations, such as hemorrhage with resultant cyst formation, calcification, vascular degenerative changes and old nodular formations.⁶⁸ The efficacy of iodine prophylaxis is greater the earlier it is applied and decreases after puberty.⁴ Consequently it would seem wisest to commence prophylaxis even before the time of conception and to maintain it throughout the pregnancy. It should be continued as well during childhood and particularly through the menarche in young girls. This can be adequately accomplished in iodine deficient goitrous regions by the continued use of iodized salt. Subsequent to the nearly worldwide preventive use of iodine a general decrease in the incidence of goiter has ensued, particularly in Switzerland, Austria, Germany, northern Italy, the United States, England, New Zealand, Poland, Rumania, Latvia and more recently in other countries.²⁴

Evident microscopic changes ordinarily occur in hyperplastic thyroids subsequent to the administration of supplemental iodine. Rapid involution of an existing hyperplasia may be induced; moreover, glandular hyperplasia of the residual tissue, even after extirpation of as much as three fourths of the thyroid, can be prevented by the administration of sufficient iodine. Marine and Lenhart even maintain that a hyperplastic gland cannot revert to the colloid state without the presence of a necessary minimum of iodine.¹⁴

68. Orr and Leitch.³ Elmer.⁶⁴

67. McClure, R. D.: Thyroid Surgery in Southern Michigan as Affected by the Generalized Use of Iodized Salt, *J. Michigan M. Soc.* 33: 58, 1934; The Incidence of Operations for Goiter in Southern Michigan; Effect of Iodized Salt After Twelve Years' General Use, *J. A. M. A.* 100: 782 (Sept. 4) 1937.

Despite almost worldwide favorable results, thus empirically substantiating the basic theory behind iodine prophylaxis, objections have been repeatedly raised, in the earlier years abroad and more recently in the United States, to the preventive use of supplemental iodine. Principal among these objections has been the harm which iodine might cause to persons with overactive thyroid glands as well as the excitation of a simple or nodular thyroid enlargement into a toxic or hyperfunctioning type. The basis of this fear of "jodbasedow," or *iodine induced hyperthyroidism*, arose as early as 1820, when Coindet treated his patients with excessive amounts of iodine.⁶⁹ The resultant idea has developed along with the subsequent progress of iodine prophylaxis. It has been a natural reaction to dangers inherent in pioneering a drug whose action was not fully understood. More recent exponents of the basic theory behind "jodbasedow" were Theodore Kocher and his successor Fritz de Quervain. In 1904 Kocher reported that patients with nodular forms of goiter may develop thyrotoxicosis when treated with iodine; in 1910 he wrote of the untoward effects of iodine in toxic diffuse goiter.⁷⁰ In 1933 de Quervain listed 33 cases of "jodbasedow" observed during a period of nine years.⁷¹

Convincing proof that iodine induced hyperthyroidism ordinarily or even commonly results from the administration of increased amounts of iodine to patients with goiter is lacking. On the other hand there is extensive evidence that supplemental iodine is ordinarily beneficial in the preventive treatment of endemic goiter. Kimball found that only 4 per cent of patients with goitrous "adenomas" later developed hyperthyroidism after the use of iodized salt, whereas 56 per cent of those with goitrous "adenomas" who used no iodized salt or any other form of iodine medication later manifested evidence of increased thyroid activity.⁷²

69. Coindet, J. R.: Découverte d'un nouveau remède contre le goitre, *Ann. de chim. et phys.* 15: 49, 1820.

70. Kocher, T.: Die Therapie des Kropfes, *Deutsche Klinik* 8: 1115, 1904; Ueber Jodbasedow, *Arch. f. klin. Chir.* 96: 403, 1910.

71. de Quervain, Fritz: Report of the Second International Goiter Conference, Berne, 1933, pp. 10-12.

72. Kimball, O. P.: The Efficiency and Safety of the Prevention of Goiter, *J. A. M. A.* 91: 454 (Aug. 18) 1928; The Prevention of Goiter in Michigan and Ohio, *ibid.* 108: 860 (March 13) 1937.

In current medical practice there is ordinarily but little hesitancy in prescribing relatively large amounts of iodide on specific indications, for example in the therapy of syphilis, without any special regard to the thyroid and its activity. Demonstrably harmful effects as a result of increased thyroid function are not expected and are rarely encountered, especially if patients with thyroid abnormalities are excluded.⁶² However, symptoms of iodism, ranging from a mild coryza or a moderate acne to a severe dermatitis even with high fever, are known to occur subsequent to the administration of iodides.⁵⁶

No ill results should be anticipated from the widespread use of iodides in the minute concentrations in which they occur in iodized salt. The development of iodism, subsequent to the continued use of iodized salt alone, has even been questioned.⁷³ Nor is iodism subsequent to the consumption of diets rich in iodine-containing foods recorded in the literature.⁷⁴

IODINE PROPHYLAXIS IN ANIMALS

Breeding difficulties among domestic animals long existed in varying degrees throughout the goiter areas of the United States.⁷⁵ A practical solution of this threat to the health of our country's live stock was found in the administration of iodine. As early as 1907 iodine-containing salts were fed to Michigan sheep in order to prevent the high death rate ordinarily occurring among the newborn.⁷⁶ In 1916 Montana, faced with a high mortality among its live stock, as well as with the development of goiter and underfunctioning thyroids, instituted similar therapy with considerable success.⁷⁷ At the University of Wisconsin Farms, since the introduction of iodized salt in 1920,

73. Campbell, W. R.: Iodine in Normal Nutrition, *Canad. M. A. J.* **40**: 77, 1939.

74. Weston, W.: Iodine in Nutrition, *Am. J. Pub. Health* **21**: 715, 1931.

75. Smith, G. E.: Iodine Requirement in the Pregnant Sow (Fetal Athyrosis), *J. Biol. Chem.* **20**: 215, 1917. Hart, E. B., and Steenbock, Harry: Thyroid Hyperplasia and the Relation of Iodine to the Hairless Pig Malady, *ibid.* **33**: 313, 1918. Kalkus, J. W.: A Study of Goiter and Associated Conditions in Domestic Animals, *Bull.* 156, Washington State Expt. Sta., July 1920. Marine.⁷⁶ Welch.⁷⁷ Shepperd.⁷⁸

76. Marine, David: On the Occurrence and Physiological Nature of Glandular Hyperplasia of the Thyroid (Dog and Sheep) Together with Remarks on Important Clinical (Human) Problems, *Bull. Johns Hopkins Hosp.* **18**: 359, 1907.

77. Welch, H.: Hairlessness and Goiter in Newborn Domestic Animals, *Bull.* 119, Montana Agr. Expt. Sta., September 1917.

there has not been an instance of goiter among the domestic animals, including sheep, swine, colts or calves.⁶⁸

Iodine prophylaxis of iodine deficiency disease among animals, or "fetal athyrosis," as it is designated, has spread to various other states and provinces. Minnesota, North and South Dakota, Wyoming, Washington, Idaho, southern Alberta and British Columbia have similarly used iodine preventively.⁷⁸

IODINE AND THE GENERAL HEALTH

Sufficient iodine is requisite for normal growth.³ As early as 1895 it was demonstrated that growth may be induced even in certain cretins by the administration of dried thyroid. A similar effect may be demonstrated in certain children, living in iodine deficient areas and not receiving supplemental iodine, who have failed to grow normally because of lesser degrees of hypothyroidism. These children may also manifest various other symptoms subsequent to varying severity of the hypothyroidism.⁷⁹

Topper and Cohen record that the administration of desiccated thyroid to normal children, as well as to children presenting evidence of hypothyroidism, resulted in definite growth acceleration in both groups.⁸⁰ Swiss statistics show that boys receiving iodine grew on the average 7 mm. more than untreated boys and put on 200 Gm. more of weight. The mean weight at birth of infants whose mothers were receiving iodized salt was 100 Gm. greater than that of control infants.³

Hunziker reported that the average height of Swiss recruits was significantly greater from 1908 to 1912 than during the period from 1884 to 1891. He concluded that supplemental iodine was partly responsible for this increase in stature. Moreover, he found the average height inversely proportional to the incidence of goiter in the sections from which the recruits came.⁸¹

78. Shepperd, J. H.: *The Northern Pig, Its Habits, Breeding and Management*, Bull. 230, North Dakota Agr. Expt. Sta., 1929. Keith, W. D.: *Goiter from the Standpoint of Prevention*, Canad. M. A. J. **16**: 1171, 1926. Meyer.⁷⁶ Smith.⁷⁶ Kalkus.⁷⁶

79. Moore, M. C., and Moseley, H. W.: *Iodine and Its Relation to Health, A Review*, New Orleans M. & S. J. **86**: 449, 1934.

80. Topper, Anne, and Cohen, Philip: *Effect of Thyroid Therapy on Children*, Am. J. Dis. Child. **35**: 205 (Feb.) 1928.

81. Hunziker, H.: *Kropf und Längenwachstum*, Schweiz. med. Wchnschr. **50**: 209, 1920.

Feeding milk with an increased iodine content to children living in a region of high goiter incidence resulted in more rapid and regular growth and development. Children with debility or those who revealed slow development, failure to gain weight or retarded growth showed subsequent steady improvement.⁸² Administration of optimal amounts of iodine to nursing animals accelerated the rate of growth and weight of their young.⁸³ Direct iodine administration to the young was likewise beneficial.⁸⁴

The favorable effect of iodine on the growth of vertebrates may be direct or indirect. It appears more likely that iodine acts indirectly by supplying the necessary constituent for normal thyroid secretion and thus permitting the gland to exert its usual function. Excessive thyroid secretion limits growth and may result in abnormal development.³

THE HUMAN REQUIREMENT OF IODINE

The human organism thus has a definite nutritive requirement for iodine. The supply necessary to answer this demand should be sufficient to meet the daily losses by excretion and to maintain within the body such a reserve as may be needed in the manufacture and distribution to the body of sufficient thyroid hormone. The amount of iodine intake, however, is not always equal to the physiologic needs. Elmer points out the contrast with the organism's chlorine requirement which is associated with the sensation of taste.²⁴ The fundamental question consequently arises: how much supplemental iodine should be supplied in goitrous areas to protect the people and live stock from the effects of iodine deficiency? Thus far, three methods have been devised in attempts to answer this question:

By the *geographic method* the iodine intake of the inhabitants of goiter free areas is determined and compared with that of goitrous areas of varying degrees. The difference in the amount of iodine intake is then

82. Weston, W.: Specially Produced Milk in the Solution of the Goiter Problem, South. M. J. 27: 249, 1934.

83. Maurer, E., and Diez, S.: Zur Kenntnis des Jods als biogenes Element: Ueber Wachstumsbeschleunigung an jungen Ratten bei Verfütterung jodangereicherter Kost an das laktierende Muttertier, Biochem. Ztschr. 183: 291, 1927. Weiser, S., and Zaltschek, A.: Zur Biochemie des Jods, ibid. 187: 377, 1927. Orr and Leitch.³

84. Hanzlik, P. J.; Talbot, E. P., and Gibson, E. E.: Continued Administration of Iodide and Other Salts; Comparative Effects on Weight and Growth of Body, Arch. Int. Med. 43: 579 (Oct.) 1928.

regarded as the amount of supplemental iodine required. According to von Fellenberg's estimate the annual iodine intake in one goitrous and one practically goiter free area in Switzerland was 4.7 and 11.4 mg. respectively.⁸⁵ Calculating from this, the iodine requirement is less than 20 micrograms daily, a figure now regarded as unusually low. Based upon a survey of the average daily urinary loss of iodine, which is an unusually accurate barometer of the iodine intake of a given area, the daily iodine requirement would lie somewhere between 100 and 200 micrograms.⁴⁹

The *principle of thyroxin formation and decay* was originally outlined by Plummer and Boothby⁸⁶ and subsequently developed by W. O. Thompson and his associates.⁸⁷ Plummer and Boothby found that the daily rate of thyroxin decay ranges between 0.2 and 0.4 mg. Thus, this daily supply of thyroxin maintained a normal basal metabolic rate in a totally myxedematous patient. Thompson and his group concluded that from 0.3 to 0.4 mg. of thyroxin was necessary to maintain a normal basal metabolic rate in myxedematous patients at bed rest. On the basis of these results the amount of thyroxin supplied daily by the thyroid to the circulation in order to maintain normal metabolic activity is equivalent to from 130 to 260 micrograms of iodine. The uncertain factor here, however, is that iodine-containing end products of thyroxin decay may be retained and eventually reutilized by the thyroid gland in the further synthesis of thyroid hormone.

Total *iodine balance studies* constitute the third principle which has been employed. The iodine balance represents the daily amount of iodine lost or retained by the body, as ascertained by the difference in the amount of iodine intake and excretion. Pioneer iodine balance determinations were accomplished by von Fellenberg,

85. von Fellenberg, T.: Das Vorkommen, der Kreislauf und der Stoffwechsel des Jods, *Ergebn. d. Physiol.* **25**: 176, 1926.

86. Plummer, H. S., and Boothby, W. M.: Specific Dynamic Action of Thyroxin, *Am. J. Physiol.* **55**: 295, 1921. Plummer, H. S.: The Interrelationship of Function of the Thyroid Gland and of Its Active Agent, Thyroxin, in the Tissues of the Body, *J. A. M. A.* **77**: 243 (July 23) 1921.

87. Thompson, W. O.; McLellan, L. L.; Thompson, Phebe K., and Dickie, L. F. N.: The Rates of Utilization of Thyroxine and of Desiccated Thyroid in Man: The Relation Between the Iodine in Desiccated Thyroid and Thyroxin, *J. Clin. Investigation* **12**: 235, 1933. Thompson, W. O.; Thompson, Phebe K.; Taylor, S. G.; Nadler, S. B., and Dickie, Lois F. N.: The Pharmacology of the Thyroid in Man, *J. A. M. A.* **104**: 972 (March 23) 1935.

who reported low values and consequently a low daily requirement.⁸⁵ The balance studies of Scheffer made in Pecs, Hungary, revealed that 54 micrograms of daily iodine intake was sufficient to maintain a normal individual in iodine balance.⁸⁸

Ohio State University studies were made on normal individuals maintained at bed rest on a monotonous diet under controlled hospital conditions (charts 1, 2 and 3). Under these circumstances the *basal* human adult iodine requirement was found to range from 44 to 75 micrograms daily and to average 67 micrograms, or approximately 1 microgram per kilogram of body weight.⁸⁹ This average daily requirement is comparable to that determined by Scheffer. However, it should be emphasized that it applies to adults maintained under controlled basal conditions. Moreover, to arrive at an optimal iodine requirement, it is necessary to take into account individual activity as well as the varied stress and strain of existence.

After consideration of the difference in iodine intake between goitrous and nongoitrous regions, as well as the amount estimated as necessary to maintain normal metabolic activity, 2 micrograms daily per kilogram of body weight, together with the daily basal requirement of 1 microgram, can be reasonably justified as an amount sufficient to account for basal needs, those of ordinary activities and also some for reserve. The optimal daily requirement would thus be somewhere near 200 micrograms for the 70 Kg. adult, a value compatible with Elmer's deduction from various investigations that the human optimal requirement ranges between 100 and 200 micrograms daily.²⁴ The pregnant woman should receive additional iodine.⁹⁰

Various methods of supplying supplemental iodine to the inhabitants of iodine deficient areas have been advanced. These include the use of foods known to be rich in iodine, iodination of water supplies, administration of iodine at regular intervals in the form of solutions or tablets, the general use of iodized salt and the consumption of iodized milk.

88. Scheffer, L.: Ueber die Jodbilanz normaler Menschen, *Biochem. Ztschr.* 259: 11, 1933.

89. Flickinger, F. M.: The Iodine Requirement of Man, Thesis for M.S. degree, Department of Surgical Research, Ohio State University, 1941. Puppel and Curtis.²⁰ Cole, Curtis and Bone.²⁰ Cole and Curtis.²⁰

90. Enright, Cole and Hitchcock.²⁰ Marine and Kimball.⁶⁴

The use of iodized salt has thus far proved the most widely adopted method. The nearly universal employment of common salt for seasoning and cooking as well as the ready preparation and low cost of iodized salt makes this a popular method. The use of milk with an increased iodine content has also been suggested as suitable, especially for children who ordinarily consume relatively large quantities.⁹¹ Effective iodine prophylaxis, however, should also conform to local conditions, since no single method will reach all those individuals who need iodine.⁹²

On June 14, 1941 the National Study Committee on Endemic Goiter, meeting in Detroit, resolved that:

On the basis of past experience in Michigan and taking into consideration more recent laboratory research, the committee recommends that for the prevention of endemic goiter the content of potassium iodide in table salt and salt for domestic animals should be 0.01 of 1 per cent, provided that an effective stabilizer be used.⁹³

The iodized salt originally recommended in 1924 by the Michigan State Medical Society in conjunction with the state board of health, and since employed in Michigan with such outstanding results, originally contained 0.02 per cent of sodium iodide, or more than twice the amount of iodine recently recommended by the National Study Committee on Endemic Goiter.⁹⁴ However, after careful consideration the committee reached the conclusion that the addition of 0.01 per cent of potassium iodide plus a stabilizer should be sufficient. The importance of a stabilizer was emphasized in view of previous experience that iodine may be lost from iodized salt and thus impart a yellow color and halogen odor due to the liberation of elemental iodine.

It has been estimated that the average adult ingests about 6.2 Gm. of salt daily. Calculated on this basis, the approximate amount of potassium iodide intake would be 620 micrograms, which is equivalent to about 474 micrograms of iodine. This is more than twice the amount we have suggested as optimal and would amply provide a person with a sufficient reserve.

The widespread prevention of endemic goiter and its sequelae will depend not only on the preparation and consumption of an adequate iodized salt but also on the persistent education of the public to its necessity.

91. Meyer.³⁰ Weston.⁷⁴

"I am sure you are aware that, in spite of the notable contributions of Michigan and the organization of similar practices in a few other states, there are still a good many states in the country where goiter is a problem with a portion of the population, where no thought is given to it, where there is no state health policy and no professional medical attitude, and where endemic goiter prevails, and in a severe form. Our interest in the American Public Health Association is to get the facts so authoritatively expressed and accepted that there can be no escape from the responsibility of the health officers to make effective all useful methods of goiter prevention. . . ." (Dr. Haven Emerson).⁶³

Under ever increasing demands of wartime effort and production each individual should have, to thrive and function at his best, among other important elements an adequate supply of iodine. For iodine, not only a nutritional necessity in the prevention of goiter, plays an important role in the general well-being of all mammals. The increased physical activity and emotional stress occurring in our struggle for survival put greatly increased demands on the human body. Thus the optimal activity essential for any all inclusive war effort cannot be maintained without a sufficient supply of iodine.

CHAPTER IX

THE TRACE ELEMENTS IN NUTRITION

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BALTIMORE

The many mineral elements which exist in animal tissues occur in widely varying amounts. They range from calcium, which comprises approximately 2 per cent of the adult human body weight and which can be expressed in kilograms, down to those which we must measure in milligrams and even micrograms, and which have been termed "trace elements." The dividing line between trace and non-trace elements is purely arbitrary and a matter of choice. Some nutritionists¹ include in the former category any element occurring in the tissues or nutritionally necessary in amounts equal to and less than iron, but others² consider only those elements below iron.

Presaging the point of view that traces of minerals might exert profound and specialized physiologic effects were the discoveries that iodine occurs in the thyroid,³ copper in octopus blood⁴ and in the hemocyanin of crustacea,⁵ zinc in the hemoscycotopin of oysters,⁶ vanadium in the blood pigment of the sea squirt⁷ and manganese in the blood of the mollusk *Pinna squamosa*.⁸

1. McCollum, E. V.; Orent-Keiles, E., and Day, H. G.: *The Newer Knowledge of Nutrition*, New York, Macmillan Company, 1939, chapter 11. Shohl, A. T.: *Mineral Metabolism*, New York, Reinhold Publishing Corporation, 1939, chapter 11.

2. Underwood, E. J.: The Significance of the "Trace Elements" in Nutrition, *Nutrition Abstr. & Rev.* **9**: 515-534 (Jan.) 1940. Godden, W.: "Trace" Elements in Human and Animal Nutrition, *J. Soc. Chem. Ind.* **58**: 791-796 (Aug.) 1939.

3. Baumann, E.: Ueber das normale Vorkommen von Jod im Thierkörper, *Ztschr. f. physiol. Chem.* **21**: 319-330, 1895-1896.

4. Harless, E.: Ueber das blaue Blut einiger wirbellosen Thiere und dessen Kupfergehalt, *Müller's Arch. Anat. Physiol.*, 1847, pp. 148-156.

5. Frédéricq, L.: Sur l'hémocyanine, substance nouvelle du sang du poulpe, *Comp. rend. Acad. d. sc.* **87**: 996, 1878.

6. Mendel, L. B., and Bradley, H. C.: Experimental Studies on the Physiology of the Mollusks, Third Paper, *Am. J. Physiol.* **17**: 167-176, 1906.

7. Henze, M.: Untersuchungen über das Blut der Ascidien: I. Vanadiumverbindung der Blutkörperchen, *Ztschr. f. physiol. Chem.* **72**: 494-501, 1911.

8. Griffiths, A. B.: *Compt. rend. Acad. d. sc.* **114**: 840, 1892, cited by von Oettingen: *Physiol. Rev.* **15**: 175-201 (April) 1935.

Nevertheless, with the exceptions of iron and iodine little physiologic significance was attached to the others of the trace elements until comparatively recently. Beginning with the investigations on their distribution, especially those of Bertrand in France, the importance of the trace elements has come to be realized, primarily through the study of experimental animals on purified diets and through the work on diseases of live stock.

The importance of iron, copper and iodine, the trace elements first demonstrated to be essential, has been discussed in previous papers. Knowledge of the mode of action of these three elements and of those discussed here indicates that the role of "traces" is one of participation in the activities of hormones and enzymes, a role, in all probability, analogous to that of the vitamins. These elements are of importance nutritionally because optimum physiologic activity requires certain of them, at least, in proper amounts. Biologic relationships are such that lack of the essential "traces" results in deficiency symptoms, while excesses result in toxic symptoms.

To date at least twenty trace elements other than iron, copper and iodine have been reported to occur, many not consistently, in animal tissues and milk.⁹ We shall discuss the elements which we consider of principal nutritional interest at this time, namely manganese, cobalt, zinc, fluorine, selenium, boron and aluminum.

MANGANESE

Conclusive evidence for the essential nature of manganese for animals was first demonstrated in 1931.¹⁰ Although earlier investigators¹¹ claimed that they had shown this fact, their results were not conclusive.

9. Dutoit, P., and Zbinden, C.: *Analyse spectrographique des cendres de sang et d'organes*, *Compt. rend. Acad. d. sc.* **188**: 1628-1629 (June) 1929. Sheldon, J. H., and Ramage, H.: *A Spectrographic Analysis of Human Tissues*, *Biochem. J.* **25**: 1608-1627, 1931. Rusoff, L. L., and Gaddum, L. W.: *The Trace Element Content of the Newborn Rat (as Determined Spectrographically)*, *J. Nutrition* **15**: 169-176 (Feb.) 1938. Wright, N. C., and Papish, J.: *The Inorganic Constituents of Milk*, *Science* **69**: 78 (Jan. 18) 1929. Blumberg, H., and Rask, O. S.: *Spectrographic Analysis of Milk Ashes*, *J. Nutrition* **6**: 285-288 (May) 1933. Drea, W. F.: *Spectrum Analysis of Milk Ashes*, *ibid.* **8**: 229-234 (Aug.) 1934; *Spectrum Analysis for Trace Elements in the Ashes of Human, Goat and Cow Milk*, *ibid.* **16**: 325-331 (Oct.) 1938. Dingle, H., and Sheldon, J. H.: *A Spectrographic Examination of the Mineral Content of Human and Other Milk*, *Biochem. J.* **32**: 1078-1086, 1938.

10. Orent and McCollum.¹² Kemmerer, Elvehjem and Hart.¹³

11. McCarrison, R.: *Effect of Manganese on Growth*, *Indian J. M. Res.* **14**: 641-648 (Jan.) 1927. Levine, V. E., and Sohm, H. A.: *The Effect of Manganese on Growth*, *J. Biol. Chem.* **59**: xlviii, 1924. McHargue, J. S.: *Further Evidence That Small Quantities of Copper, Manganese and Zinc Are Factors in the Metabolism of Animals*, *Am. J. Physiol.* **77**: 245-255 (July) 1926.

Orent and McCollum¹² found that male rats reared from weaning on a diet adequate except for manganese developed sterility and testicular degeneration after ninety days. Females on the same diet delivered young which survived but a short while; in addition they failed to suckle normal stock young. Hemoglobin regeneration, estrus and growth were not affected by the deficiency.

When mice were reared on a manganese low diet consisting of whole milk supplemented with iron and copper, decreased growth and an abnormal estrus cycle resulted.¹³

Daniels and Everson¹⁴ fed a manganese deficient mineralized milk diet to rats and confirmed the fact that the females produced nonviable young. However, their findings differed from those of Orent and McCollum¹² in that the deficient females suckled normal foster young.

Recently we¹⁵ found that manganese is essential for the normal growth of the rat. The symptoms of deficiency in the female's production of nonviable young can be cured as well as prevented by manganese. In accord with the findings of Daniels and Everson¹⁴ the deficient females, while losing their own young, could suckle normal foster young. The few young which did survive to weaning uniformly showed weakness and incoordination most pronounced in the third week of life, with poor growth and poor equilibration persisting throughout life. Manganese is needed for the proper development of other functions in addition to the reproductive. Boyer and co-workers^{15a} have likewise found that manganese is essential for growth in the rat. Using a mineralized milk diet they observed the symptoms obtained in mice on a similar diet¹³ and in addition, a marked delay in the opening of the vaginal orifice.

12. Orent, E. R., and McCollum, E. V.: Effects of Deprivation of Manganese in the Rat, *J. Biol. Chem.* **92**: 651-678 (Aug.) 1931.

13. Kemmerer, A. R.; Elvehjem, C. A., and Hart, E. B.: Studies on the Relation of Manganese to the Nutrition of the Mouse, *J. Biol. Chem.* **92**: 623-630 (Aug.) 1931.

14. Daniels, Amy L., and Everson, Gladys, J.: The Relation of Manganese to Congenital Debility, *J. Nutrition* **9**: 191-203 (Feb.) 1935.

15. Shils, M. E., and McCollum, E. V., to be published.

15a. Boyer, P. D.; Shaw, J. J., and Phillips, P. H.: Studies on Manganese Deficiency in the Rat, *J. Biol. Chem.* **143**: 417-425 (April) 1942.

The differing findings of the Hopkins and Wisconsin workers on the reproductive ability of the deficient rats and mice is probably explained on the basis of differences in the magnesium content of the diets used. Purified diets have not yet been brought as low as whole milk in manganese content. If this is true, then different symptoms occur at different levels of intake. It is possible that unknown dietary relationships might also have caused the differences.

The species differences in deficiency symptoms and requirement, of which we are well aware in the case of the vitamins, extends to the trace elements. Investigations of manganese deficiency in chickens have resulted in knowledge of practical importance. The requirements of this species are much higher than those of any mammal studied and the most manifest symptoms are different. Manganese has been shown¹⁶ to prevent the development of an osteodystrophy of chickens called perosis. The symptoms are enlargement of the tibial-metatarsal joint, twisting and bending of the distal end of the tibia and of the proximal end of the tarsometatarsus and slipping of the gastrocnemius tendon from its condyles, resulting in severe crippling. The deficient chicks have shortened leg bones¹⁷ and vertebral columns.¹⁸

It has long been known that excess calcium and phosphorus in the diet intensify perosis and that injected manganese is more efficiently utilized than that given orally. In vitro and in vivo experiments¹⁹ have helped explain these observations by showing that manganese is removed from solution by insoluble calcium phosphate or by ferric hydroxide and so rendered unavailable.

The chick embryo, like that of the rat, requires manganese for normal development. Lyons and Insko²⁰

16. Wilgus, H. S., Jr.; Norris, L. C., and Heuser, G. F.: The Role of Manganese and Certain Other Trace Elements in the Prevention of Perosis, *J. Nutrition* **14**: 155-167 (Aug.) 1937.

17. Gallup, W. D., and Norris, L. C.: Essentialness of Manganese for Normal Development of Bone, *Science* **87**: 18-19 (Jan. 7) 1938. Caskey, Gallup and Norris.¹⁸

18. Caskey, C. D.; Gallup, W. D., and Norris, L. C.: The Need for Manganese in the Bone Development of the Chick, *J. Nutrition* **17**: 407-417 (May) 1939.

19. Wilgus, H. S., Jr., and Patton, A. R.: Factors Affecting Manganese Utilization in the Chick, *J. Nutrition* **18**: 35-45 (July) 1939.

20. Lyons, M., and Insko, W. M., Jr.: Chondrodystrophy in the Chick Embryo Produced by a Mineral Deficiency in the Diet of the Hen, *Poultry Sc.* **16**: 365-366 (Sept.) 1937.

observed a very low hatchability of eggs of deficient hens; the embryos which developed sufficiently were chondrodystrophic and the few which hatched also had shortened leg and wing bones (micromelia). Injection of manganese into the eggs prior to incubation resulted in normal development. Caskey and Norris²¹ have observed an ataxia accompanying the micromelia.

The fact that only slight differences in manganese content are found between the decidedly different bones¹⁹ and egg shells²² of normal and manganese deficient chickens is indication that probably manganese plays some indirect or catalytic role in calcium and phosphorus metabolism. The possibility of manganese deficiency as a factor in producing bone abnormality in rats²³ and lameness in pigs²⁴ has been pointed out.

The specificity of manganese as the inorganic factor preventing perosis has been demonstrated.²⁵ However, the discovery that deficiencies of choline²⁶ and of biotin^{26a} result in perosis in fowl is an indication that there are other factors necessary to prevent abnormal bone metabolism resulting in perosis. Perotic malformation may occur as a result of stress and strain on the retarded and abnormal bones of the deficient animal.^{26b} It is suggested^{26b} that the symptoms of "slipped epiphyses" in children^{26c} resemble those of perosis. Biochemical and histologic comparisons of these bone abnormalities would be of interest.

21. Norris, I. C., and Caskey, C. D.: A Chronic Congenital Ataxia and Osteodystrophy in Chicks Due to Manganese Deficiency, *J. Nutrition* **17**: 16-17, 1939, *Proc. Caskey, C. D., and Norris, I. C.: Micromelia in Adult Fowl Caused by Manganese Deficiency During Embryonic Development, Proc. Soc. Exper. Biol. & Med.* **44**: 332-335 (June) 1940.

22. Caskey, C. D., and Norris, I. C.: Further Studies on the Role of Manganese in Poultry Nutrition, *Poultry Sc.* **17**: 433, 1938, *Proc.*

23. Barnes, L. L.; Sperling, G., and Maynard, L. A.: Bone Development in the Albino Rat on a Low Manganese Diet, *Proc. Soc. Exper. Biol. & Med.* **46**: 562-565 (April) 1941.

24. Miller, R. C.; Keith, T. B.; McCarty, M. A., and Thorp, W. T. S.: Manganese as a Possible Factor Influencing the Occurrence of Lameness in Pigs, *Proc. Soc. Exper. Biol. & Med.* **45**: 50-51 (Oct.) 1940.

25. Lyons, M.; Insko, W. M., Jr., and Martin, J. H.: The Effect of Intraperitoneal Injections of Manganese, Zinc, Aluminum and Iron Salts on the Occurrence of Slipped Tendon in Chicks, *Poultry Sc.* **17**: 12-16 (Jan.) 1938; The Effect of Manganese, Zinc, Aluminum and Iron Salts on the Incidence of Perosis in Chicks, *ibid.* **17**: 264-269 (July) 1938.

26. Jukes, T. H.: Effect of Choline and Other Supplements on Perosis, *J. Nutrition* **20**: 445-458 (Nov.) 1940.

26a. Jukes, T. H., and Bird, F. H.: Prevention of Perosis by Biotin, *Proc. Soc. Exper. Biol. & Med.* **49**: 231-232 (Feb.) 1942.

26b. Combs, G. F.; Norris, I. C., and Heuser, G. F.: The Interrelationship of Manganese, Phosphatase, and Vitamin D in Bone Development, *J. Nutrition* **28**: 131-140 (Feb.) 1942.

26c. Ghormley, R. K., and Fairchild, R. D.: The Diagnosis and Treatment of Slipped Epiphyses, *J. A. M. A.* **114**: 229-235 (Jan. 20) 1940.

A relationship between manganese and thiamine has been postulated.²⁷ Large amounts of thiamine or manganese given to rats caused reproduction and lactation failures which could be prevented by increasing the intake of the other of the two substances.²⁸ In addition, rats on a thiamine low diet receiving excess manganese were more quickly depleted than those not receiving it.²⁹ The implications of the work merit its being repeated.

That the need for manganese is widespread is indicated by the fact that, in addition to the animal species already discussed, it has been found essential for plants,³⁰ including fungi³¹ and several bacteria.³²

There is no definite information about the human requirements for manganese nor is there evidence of deficiency ever occurring in man. Everson and Daniels,³³ on the basis of balance studies, suggest that the diet of preschool age children should contain between 0.20 and 0.30 mg. of manganese per kilogram of body weight; retention in children 8 to 12 years of age was only 0.02 ± 0.22 mg. daily.³⁴ Approximately 4 mg. is found in the daily adult human diet³⁵ and substantially equivalent amounts are excreted. The manganese content of various foods has been determined, and it is apparent that plant foodstuffs are the chief source in the diet.³⁶ It occurs regularly in the

27. Perla and Sandberg.²⁸ Sandberg, Perla and Holly.²⁹

28. Perla, D., and Sandberg, M.: Metabolic Interdependence of Vitamin B₁ and Manganese: Reciprocal Neutralization of Their Toxic Effects, *Proc. Soc. Exper. Biol. & Med.* **41**: 522-527 (June) 1939.

29. Sandberg, M.; Perla, D., and Holly, O. M.: Interdependence of Vitamin B₁ and Manganese; Manganese, Copper and Iron Metabolism in B₁ Deficient Rats, *ibid.* **42**: 368-371 (Nov.) 1939.

30. Collison, R. C.: Minor Elements and Crop Fertilization, New York (Geneva) Agr. Expt. Sta. Circ. 168, 1937, pp. 1-13.

31. Steinberg, R. A.: Growth of Fungi in Synthetic Nutrient Solutions, *Botan. Rev.* **5**: 327-350 (June) 1939.

32. Woolley, D. W.: Manganese and the Growth of Lactic Acid Bacteria, *J. Biol. Chem.* **140**: 311-312 (July) 1941.

33. Everson, Gladys J., and Daniels, Amy L.: A Study of Manganese Retentions in Children, *J. Nutrition* **8**: 497-502 (Nov.) 1934.

34. Macy, Icie G.: Nutrition and Chemical Growth in Childhood, Springfield, Ill., Charles C. Thomas, 1942, vol 1, Evaluation, chapter 3.

35. Kehoe, R. A.; Cholak, J., and Story, R. V.: Manganese, Lead, Tin, Aluminum, Copper and Silver in Normal Biological Material, *J. Nutrition* **20**: 85-98 (July) 1940.

36. Remington, R. E., and Shiver, H. E.: Iron, Copper and Manganese Content of Some Common Vegetables, *J. A. Off. Agr. Chem.* **13**: 129-132, 1930. Hodges, Mildred A., and Peterson, W. H.: Manganese, Copper and Iron Content of Serving Portions of Common Foods, *J. Am. Dietet. A.* **7**: 6-16 (June) 1931. Lindow, C. W., and Peterson, W. H.: The Manganese Content of Plant and Animal Materials, *J. Biol. Chem.* **75**: 169-175 (Oct.) 1927. Peterson, W. H., and Skinner, J. T.: Distribution of Manganese in Foods, *J. Nutrition* **4**: 419-426 (Sept.) 1931.

tissues of animals, with liver containing the greatest amount.³⁷ There is a great rise in the percentage of manganese in the human fetal liver during the last months of pregnancy.³⁸

After oral, subcutaneous or intraperitoneal administration, manganese is excreted almost entirely in the feces with only small amounts being excreted in the urine.³⁹

After the necessity for copper as a complement to iron in hemoglobin formation had been established,⁴⁰ a controversy arose as to whether certain other elements could replace copper in this important function. Some investigators⁴¹ have claimed that manganese could, but today the evidence to the contrary is quite conclusive.⁴²

Acute and chronic manganese poisoning in man and experimental animals has been reviewed.⁴³

Manganese and Enzyme Activity.—Since Bertrand in 1897 first implicated manganese⁴⁴ (erroneously, as we now know⁴⁵) as the activator of the oxidase laccase, this element has been found to activate a number of enzymes.

Of particular interest is the observation of Wiese and his co-workers⁴⁶ that manganese deficient chicks

37. Kehoe, R. A.; Cholak, J., and Story, R. V.: Spectrochemical Study of the Normal Ranges of Concentration of Certain Trace Metals in Biological Materials, *J. Nutrition* **19**: 579-592 (June) 1940.

38. Ramage, H.; Sheldon, J. H., and Sheldon, W.: A Spectrographic Investigation of the Metallic Content of the Liver in Childhood, *Proc. Roy. Soc.* **113**: 308-327 (Aug.) 1933. Gruzewska, Z. (Mme.), and Roussel, G.: Le manganèse dans le foie foetal au cours de son développement, *Bull. Soc. chim. biol.* **21**: 730-736 (May) 1939.

39. Skinner, J. T.; Peterson, W. H., and Steenbock, Harry: The Manganese Metabolism of the Rat, *J. Biol. Chem.* **90**: 65-80 (Jan.) 1931. Greenberg, D. M., and Campbell, W. W.: Studies in Mineral Metabolism with the Aid of Induced Radioactive Isotopes: IV. Manganese, *Proc. Nat. Acad. Sc.* **26**: 448-452 (July) 1940. Kent and McCance.⁴⁰

40. Hart, E. B.; Steenbock, Harry; Waddell, J., and Elvehjem, C. A.: Iron in Nutrition: Copper as a Supplement to Iron for Hemoglobin Building in the Rat, *J. Biol. Chem.* **77**: 797-812 (May) 1928.

41. Titus, R. W.; Cave, H. W., and Hughes, J. S.: Manganese-Copper-Iron Complex as a Factor in Hemoglobin Building, *J. Biol. Chem.* **80**: 565-570 (Dec.) 1928. Myers, V. C., and Beard, H. H.: The Influence of Inorganic Elements on Blood Regeneration in Nutritional Anemia, *J. A. M. A.* **93**: 1210-1212 (Oct. 19) 1929.

42. Elvehjem, C. A.: Biological Significance of Copper and Its Relation to Iron Metabolism, *Physiol. Rev.* **15**: 471-507 (July) 1935.

43. von Oettingen, W. F.: Manganese: Its Distribution, Pharmacology and Health Hazards, *Physiol. Rev.* **15**: 175-201 (April) 1935.

44. Bertrand, G.: Sur l'intervention du manganèse dans les oxydations provoqués par la laccase, *Compt. rend. Acad. d. sc.* **124**: 1032-1035, 1897.

45. Keilin, D., and Mann, T.: Laccase, a Blue Copper-Protein Oxidase from the Latex of *Rhus Succedanea*, *Nature* **143**: 23 (Jan. 7) 1939.

46. Wiese, A. C.; Johnson, B. C.; Elvehjem, C. A.; Hart, E. B., and Halpin, J. G.: A Study of Blood and Bone Phosphatase in Chick Perosis, *J. Biol. Chem.* **127**: 411-420 (Feb.) 1939.

with perosis have a lower blood and bone phosphatase activity than normal birds and that the decrease in phosphatase activity precedes the appearance of perotic symptoms. This decreased activity may be due not only to decreased manganese concentration but also to an actual decrease in the amount of enzyme present.⁴⁷

In in vitro experiments manganese has been found to activate not only blood and bone phosphatases⁴⁷ but also the phosphatases in liver,⁴⁸ yeast,⁴⁹ intestine and kidney⁵⁰ and, although other divalent ions (magnesium, cobalt and iron) also activate phosphatases, they are not as effective in most cases as manganese.

Another enzyme with which manganese has been implicated is arginase, which is accepted as playing an important role in the formation of urea.⁵¹ The strong activating effect of manganese on this enzyme led Edlbacher and Pinösch⁵² to postulate that it is a protein-manganese complex. Richards and Hellerman⁵³ have given more definite evidence for the possibility that manganese is the physiologic activating ion, although cobalt and nickel can produce high activity in vitro. The evidence for the in vivo activity of manganese has been strengthened by the demonstration of a decrease in the arginase activity of manganese deficient rats.^{53a}

Among the other enzymes whose activity increases with the addition of manganous ions are (a) phosphoglucomutase⁵⁴ (which causes a transfer of phosphate from carbon atom 1 of glucose-1-phosphate to carbon atom 6 in carbohydrate metabolism, (b) intestinal

47. Wiese, A. C.; Benham, G. H.; Elvehjem, C. A., and Hart, E. B.: Further Bone Phosphatase Studies in Chick Perosis, *Poultry Sc.* **20**: 255-258 (May) 1941.

48. Bamann, E., and Heumüller, E.: Ueber die Aktivierung von Phosphatase durch verschiedene Metall-Ionen, *Naturwissensch.* **28**: 535 (Aug. 16) 1940. Cloetens.⁵⁰

49. Massart, L., and Dufait, R.: Fluoridhemmung und Metallaktivierung der Hefephosphatase, *Naturwissensch.* **27**: 806-807 (Dec. 1) 1939.

50. Cloetens, R.: Aktivierung und Hemmung der alkalischen Phosphatase, *Naturwissensch.* **27**: 806 (Dec. 1) 1939.

51. Krebs, H. A., and Henseleit, K.: Untersuchungen über die Harnstoffbildung im Tierkörper, *Ztschr. f. physiol. Chem.* **210**: 33-66. 1932.

52. Edlbacher, S., and Pinösch, H.: Ueber die Natur der Arginase, *Ztschr. f. physiol. Chem.* **250**: 241-248, 1937.

53. Richards, Marianna M., and Hellerman, L.: Purified Liver Arginase; Reversible Inactivation and Reactivation, *J. Biol. Chem.* **134**: 237-252 (June) 1940.

53a. Shils and McCollum.³⁵ Boyer, Shaw and Phillips.^{15a}

54. Cori, G. T.; Colowick, S. P., and Cori, C. F.: The Enzymatic Conversion of Glucose-1-phosphoric Ester to 6-ester in Tissue Extracts, *J. Biol. Chem.* **124**: 543-555 (July) 1938.

peptidases,⁵⁵ (c) cholinesterase,⁵⁶ (d) cozymase,⁵⁷ (e) isocitric dehydrogenase⁵⁸ (which catalyzes the reaction: isocitric acid to α ketoglutaric acid) and (f) yeast and animal carboxylase,⁵⁹ which contain diphosphothiamine. In yeast carboxylase, magnesium appears to be the naturally occurring activating ion, but in vitro manganese can quantitatively replace it. (g) The adenosinetriphosphatase activity of the muscle protein, myosin^{59a} has been found to be activated strongly by calcium and manganese.^{59b} All the enzymes listed are activated in vitro by one or more divalent ions in addition to manganese. The determination of the naturally activating metallic ion or ions and the manner of their action may be of value.

Rudra⁶⁰ has found the presence of manganese necessary for the in vitro and in vivo synthesis of a reducing substance, presumably ascorbic acid, by rats and guinea pigs and their tissues. As yet there are no reports of scorbutic symptoms in animals on manganese low diets.⁶¹ Furthermore, it has been found that in manganese deficiency in the rat there is no lowering of the ascorbic acid content of various tissues;^{15a} Rudra's findings were not substantiated.^{15a}

COBALT

Our present knowledge of cobalt indicates that it is essential for at least several animal species and occurs

55. Berger, J., and Johnson, M. J.: Metal Activation of Peptidases, *J. Biol. Chem.* **130**: 641-654 (Oct.) 1939. Smith, E. L., and Bergmann, M.: The Activation of Intestinal Peptidases by Manganese, *ibid.* **138**: 789-790 (April) 1941.

56. Massart, L., and Dufait, R.: Activations et inhibitions de la cholinesterase, *Enzymologia* **6**: 282-286, 1939. Nachmansohn, D.: Action of Ions on Choline Esterase, *Nature* **145**: 513-514 (March 30) 1940.

57. Ohlmeyer, P., and Ochoa, S.: Ueber die Rolle des Mangans für die Phosphat übertragende Funktion der Cozymase, *Naturwissensch.* **25**: 253 (April 16) 1937.

58. Adler, E.; von Euler, H.; Günther, G., and Plass, M.: Isocitric Dehydrogenase and Glutamic Acid Synthesis in Animal Tissues, *Biochem. J.* **33**: 1028-1045, 1939.

59. Green, D. E.; Herbert, D., and Subrahmanyam, V.: Carboxylase, *J. Biol. Chem.* **138**: 327-339 (March) 1941. Green, D. E.; Westfeld, W. W.; Vennesland, B., and Knox, W. E.: Pyruvic and Ketoglutaric Carboxylases of Animal Tissues, *ibid.* **140**: 683-684 (Aug.) 1941.

59a. Engelhardt, W. A., and Liubimowa, M. N.: Myosine and Adenosinetriphosphatase, *Nature* **144**: 668-669 (Oct. 14) 1939.

59b. Bailey, K.: Myosin and Adenosinetriphosphatase, *Biochem. J.* **36**: 121-139 (Feb.) 1942.

60. Rudra, M. N.: Role of Manganese in the Biological Synthesis of Ascorbic Acid, *Nature* **144**: 868 (Nov. 18) 1939.

61. Orent and McCollum,¹³ Kemmerer, Elvehjem and Hart,¹² Daniels and Everson,¹⁴ Shils and McCollum,¹⁵ Boyer, Shaw and Phillips,^{15a}

62. Footnote deleted on proof.

in both plant and animal tissues in very small amounts.⁶³ Its distribution in animal tissues has been recently determined again by the use of the radioactive form⁶⁴ and confirmatory evidence obtained that it occurs in highest concentrations in glandular organs, especially the pancreas, liver, spleen and kidneys. Absorbed or injected cobalt, unlike manganese, is excreted in the urine, but the greater part of ingested cobalt is not absorbed.⁶⁵

Bertrand,⁶⁶ on finding that the pancreas is relatively high in cobalt and nickel, suggested that these metals might be connected with the synthesis of insulin. He claimed a prolongation of insulin hypoglycemia on injection of cobalt; nickel had less effect. This effect of cobalt has not been confirmed.⁶⁷ Nickel has more recently been found to delay insulin hypoglycemia.⁶⁸ However, a number of metal salts have been found to influence the onset and extent of insulin hypoglycemia, notably zinc, so that such action is not specific.

A peculiar property of cobalt (in either metallic or ionic form) is its ability to produce a polycythemia when ingested or injected.⁶⁹ This cobalt polycythemia has been produced in rats, mice, guinea pigs, rabbits, dogs, pigs, chickens and frogs. Indicative of the small concentrations in which cobalt acts is the fact that 0.04 to 0.05 mg. in the entire body of a rat is sufficient to produce polycythemia.⁷⁰ It is a true polycythemia with an increased blood volume resulting from the increase in red blood cells and with little alteration

63. Ahmad, B., and McCollum, E. V.: The Cobalt Content of Some Food Materials from Different Parts of the United States, *Am. J. Hyg.* **29**: 24-26 (Jan.) 1939. Copp and Greenberg.⁶⁴

64. Copp, D. H., and Greenberg, D. M.: Studies in Mineral Metabolism with the Aid of Artificial Radioactive Isotopes: VI. Cobalt, *Proc. Nat. Acad. Sc.* **27**: 153-157 (March) 1941.

65. Kent, N. L., and McCance, R.: The Absorption and Excretion of "Minor" Elements by Man: 2. Cobalt, Nickel, Tin and Manganese, *Biochem. J.* **35**: 877-883 (Sept.) 1941. Copp and Greenberg.⁶⁴

66. Bertrand, G.: The Importance of Minute Chemical Constituents of Biological Products: Nickel, Cobalt and Insulin, *Science* **64**: 629-630 (Dec. 26) 1926.

67. Blatherwick, N. R., and Sahyun, M.: The Effect of Cobalt on Insulin Hypoglycemia in Rabbits, *Am. J. Physiol.* **81**: 560-562 (Aug.) 1927. Magenta, M. A.: Action des sels de nickel et de cobalt sur l'hypoglycémie insulinaire, *Compt. rend. Soc. de biol.* **93**: 169-170 (Jan. 20) 1928. Scott and Fisher.⁶⁸

68. Scott, D. A., and Fisher, A. M.: The Effect of Zinc Salts on the Action of Insulin, *J. Pharmacol. & Exper. Therap.* **55**: 206-221 (Oct.) 1935.

69. Waltner, Klara, and Waltner, K.: Kobalt und Blut, *Klin. Wchnschr.* **8**: 313 (Feb. 12) 1929.

70. Stare, F. J., and Elvehjem, C. A.: Cobalt in Animal Nutrition, *J. Biol. Chem.* **99**: 473-483 (Jan.) 1933.

in the total and differential leukocyte counts.⁷¹ The action of cobalt appears to be on the erythropoietic centers, since hyperplasia⁷² and stimulation of the erythrocytic precursors in the bone marrow⁷³ and an initial increase in reticulocytes⁷⁴ have been observed following its administration. The spleen plays no essential role in the phenomenon. The polycythemia has been maintained for months in dogs⁷⁵ and rats.⁷⁶

Ascorbic acid can prevent or reduce the polycythemia of cobalt in rabbits⁷⁷ and dogs⁷⁸ but has no effect on that produced by anoxia.⁷⁵ Liver, choline and certain vasodilator drugs have also been found effective in reducing the level of cobalt polycythemia in dogs.⁷⁸ When fed to rats, liver did not reduce cobalt polycythemia but, on the contrary, increased it.⁷⁹

The interesting observation has been made recently that the sulfur containing amino acids, methionine, cystine and cysteine, particularly the latter, prevent the toxic effects induced by cobalt and nickel administration.^{79a}

Frost and his collaborators⁸⁰ have found that the polycythemia of adult dogs on a mineralized milk diet supplemented with cobalt is only temporary; in young

71. Orten, J. M.; Underhill, F. A.; Mugrage, E. R., and Lewis, R. C.: Polycythemia in the Rat on a Milk-Iron-Copper Diet Supplemented by Cobalt, *J. Biol. Chem.* **96**:11-16 (April) 1932. Orten, Underhill, Mugrage and Lewis.⁷⁶

72. Mascherpa, P.: Le pouvoir hématopoïétique du cobalt, *Arch. ital. de Biol.* **82**:112-120, 1930.

73. Kleinberg, W.; Gordon, A. S., and Charipper, H. A.: Effect of Cobalt on Erythropoiesis in Anemic Rabbits, *Proc. Soc. Exper. Biol. & Med.* **42**:119-120 (Oct.) 1939.

74. Orten, J. M.: On the Mechanism of the Hematopoietic Action of Cobalt, *Am. J. Physiol.* **114**:414-422 (Jan.) 1936.

75. Davis, J. E.: The Effect of Ascorbic Acid Administration on Experimental Polycythemia: The Mechanism of Cobalt Polycythemia, *Am. J. Physiol.* **129**:140-145 (April) 1940.

76. Orten, J. M.; Underhill, F. M.; Mugrage, E. R., and Lewis, R. C.: The Effect of Manganese on Cobalt Polycythemia, *J. Biol. Chem.* **99**:465-468 (Jan.) 1933.

77. Barron, A. G., and Barron, E. S. G.: Mechanism of Cobalt Polycythemia: Effect of Ascorbic Acid, *Proc. Soc. Exper. Biol. & Med.* **35**:407-409 (Dec.) 1936.

78. Davis, J. E.: Depression of Experimental Polycythemia by Choline Hydrochloride or Liver Administration, *Am. J. Physiol.* **127**:322-327 (Sept.) 1939; The Depression of Experimental Polycythemia by Various Substances in Dogs, Rabbits and Man, *J. Pharmacol. & Exper. Therap.* **73**:162-169 (Oct.) 1941.

79. Anderson, H. D.; Underwood, E. J., and Elvehjem, C. A.: Factors Affecting the Maintenance of Cobalt Polycythemia in the Rat, *Am. J. Physiol.* **130**:373-378 (Aug.) 1940.

79a. Griffith, W. H.; Pavcek, P. L., and Mulford, D. J.: The Relation of the Sulfur Amino Acids to the Toxicity of Cobalt and Nickel in the Rat, *J. Nutrition* **23**:603-612 (June) 1942.

80. Frost, D. V.; Spitzer, E. H.; Elvehjem, C. A., and Hart, E. B.: Some Effects of Cobalt and Liver Substance on Blood Building in Dogs, *Am. J. Physiol.* **134**:746-754 (Nov.) 1941.

dogs cobalt has more toxic effect with little influence on the blood picture.

Copper deficient rats fail to develop polycythemia when fed cobalt.⁷⁶ Schultze⁸² has shown that cytochrome oxidase activity is diminished in copper deficient rats and fails to respond to cobalt alone, whereas the feeding of cobalt to animals receiving copper causes a rapid increase in the cytochrome oxidase activity in the bone marrow.

The knowledge that cobalt is a biologic essential is the result of research carried out in Australia and New Zealand. The story of this work has been reviewed in some detail recently;⁸³ consequently, only a brief summary is needed here.

In certain parts of the world cattle and sheep have been afflicted for long periods with a disease manifested by progressive emaciation and anemia. Western Australia has had its "Denmark disease" or enzootic marasmus, South Australia its "coast disease," New Zealand its "bush sickness," Scotland its "pine disease," Kenya its "nakruitis" and Florida its "salt sickness."

Deficiency of iron had been regarded as the cause of all these diseases for some years, but in 1933 this view was questioned because of the unevenness in response to various iron compounds. In addition, Underwood⁸⁴ in 1934 discovered that the livers and spleens of affected animals contained excessive amounts of iron, hardly a condition associated with deficient iron intake. The iron deficiency theory was completely discredited by Filmer and Underwood,⁸⁵ who demonstrated that by using an iron free extract of limonite, a hydrated ferric oxide used extensively in treatment, they could cure enzootic marasmus, implicating some contaminant of the iron compound as the curative factor. In 1935 Marston⁸⁶ and Lines⁸⁷ and almost simultaneously

82. Schultze, M. O.: The Relation of Copper to Cytochrome Oxidase and Hematopoietic Activity of the Bone Marrow of Rats, *J. Biol. Chem.* **138**: 219-224 (March) 1941.

83. Underwood, E. J.: The Significance of the "Trace Elements" in Nutrition, *Nutrition Abstr. & Rev.* **9**: 515-534 (Jan.) 1940. Marston, Lines, Thomas and McDonald.⁸⁴

84. Underwood, E. J.: Enzootic Marasmus Iron Content of Liver, Kidney and Spleen, *Australian Vet. J.* **10**: 87-92, 1934.

85. Filmer, J. F., and Underwood, E. J.: Enzootic Marasmus: Treatment with Limonite Fractions, *Australian Vet. J.* **10**: 83-87, 1934.

86. Marston, H. R.: Problems Associated with "Coast Disease" in South Australia, *Comm. Austral. J. Coun. Sc. Ind. Res.* **8**: 111-116 (May) 1935.

87. Lines, E. W.: The Effect of the Ingestion of Minute Quantities of Cobalt by Sheep Affected with "Coast Disease": A Preliminary Note, *Comm. Austral. J. Coun. Sc. Ind. Res.* **8**: 117 (May) 1935.

Underwood and Filmer⁸⁸ found that cobalt was the curative agent in "coast disease" and enzootic marasmus. Lines⁸⁷ and Marston⁸⁶ had been led to try cobalt through the Waltner's⁶⁰ work on cobalt polycythemia. In 1936 Askew and Dixon⁸⁹ in New Zealand found cobalt effective in the treatment of bush sickness. Cattle and sheep suffering from Florida salt sickness,⁹⁰ Kenya nakruitis⁹¹ and Scotch pine sickness⁹² have since been treated successfully with small amounts of cobalt. Certain areas of western Canada and of Michigan are now reported to have sheep suffering with cobalt deficiency.⁹³ The deficiency may be complicated by a lack of other elements. Salt sickness may be associated with an iron and copper deficiency, and there have been sporadic outbreaks in areas with coast disease of an ataxia in young lambs resulting from central nervous system degeneration which can be prevented by administration of copper.⁹⁴

Demonstrating once more the quantitative or perhaps qualitative differences in requirement for trace elements that exist among different species is the fact that horses can remain healthy on cobalt low pastures on which sheep and cattle develop severe deficiency symptoms. Cobalt deficiency has as yet not been produced in rats even with daily intakes as low as 0.0006 mg. of cobalt;⁹⁵ this element may be essential to this species but in still smaller amounts.

The anemia that developed in rats on a whole milk diet responded no better to administration of iron,

88. Underwood, E. J., and Filmer, J. F.: The Determination of the Biologically Potent Element Cobalt in Limonite, Australian Vet. J. **11**: 84-92, 1935.

89. Askew, H. O., and Dixon, J. K.: The Importance of Cobalt in the Treatment of Certain Stock Ailments in the South Island, New Zealand, New Zealand J. Sc. Technol. **18**: 73-84 (July) 1936.

90. Neal, W. M., and Ahmann, C. F.: The Essentiality of Cobalt in Bovine Nutrition, J. Dairy Sc. **20**: 741-753, 1937.

91. Ann. Repts. Dept. Agr. Kenya 1936, 1937; cited by Underwood.⁸⁸

92. Corner, H. H., and Smith, A. M.: The Influence of Cobalt on Pine Disease in Sheep, Biochem. J. **32**: 1800-1805 (Oct.) 1938.

93. Bowstead, J. E., and Sackville, J. P.: Studies with a Deficient Ration for Sheep: 2. Effects of Cobalt Supplement, Canad. J. Res. D. **17**: 15, 1939; through Nutrition Abstr. & Rev. **9**: 241, 1939. Balzer, A. C.; Killham, B. J.; Duncan, C. W., and Huffman, C. F.: Cobalt Deficiency Disease Observed in Some Michigan Dairy Cattle, Michigan Agri. Exper. Sta. Quart. Bull. **24**: 68-70 (Aug.) 1941.

94. Marston, H. R.; Lines, E. W.; Thomas, R. G., and McDonald, I. W.: Cobalt and Copper in Ruminant Nutrition, Nature **141**: 398 400 (March 5) 1938.

95. Underwood, E. J., and Elvehjem, C. A.: Is Cobalt of Any Significance in the Treatment of Milk Anemia with Iron and Copper? J. Biol. Chem. **124**: 419-424 (July) 1938.

copper and cobalt than to iron and copper alone.⁹⁵ The results when dogs were used were not so simple;⁹⁶ in many cases iron and copper alone were able to cure the anemia produced by restriction to a whole milk diet or by hemorrhage, but, in about an equal number of dogs treated with iron and copper in which blood regeneration was unusually slow, small amounts of cobalt stimulated hemopoiesis.

The requirements for cobalt by man are unknown. The use of this element in the treatment of human anemia has been reported for children⁹⁷ with some favorable results and for adults⁹⁸ with negative results. The adult cases were very few in number. Waltner⁹⁹ has reported that in children, in contrast to experimental animals, cobalt administration results in an increase in the erythrocyte count but in no increase in hemoglobin.

Cobalt shares with manganese the ability to activate in vitro a number of enzymes.¹⁰⁰ It has not been implicated as the physiologic ion in any enzyme system.

ZINC

Although several of the earlier investigators¹⁰¹ claimed to have shown the importance of zinc in nutrition, unequivocal proof for its necessity awaited the work of Todd, Elvehjem and Hart¹⁰² in 1934. Using a diet containing only 1.6 parts per million of zinc, they found that the growth of the deficient rats was much inferior to the controls and that an alopecia developed over various parts of the body. With still more effec-

96. Frost, D. V.; Elvehjem, C. A., and Hart, E. B.: A Study of the Need for Cobalt in Dogs on Milk Diets, *J. Nutrition* **21**: 93-100 (Jan.) 1941.

97. Kato, K.: Iron-Cobalt Treatment of Physiologic and Nutritional Anemia in Infants, *J. Pediat.* **11**: 385-396 (Sept.) 1937. Waltner.⁹⁹

98. Baxter, C. R.: Copper and Cobalt in Anemia, *Brit. M. J.* **1**: 534-535 (March 11) 1939. Cronin, E.: Copper and Cobalt in Anemia, *ibid.* **1**: 643 (March 25) 1939.

99. Waltner, K.: Therapeutische Versuche mit Kobalt, *Acta pediat.* **11**: 438-440 (Aug.) 1930.

100. See section on manganese.

101. Bertrand, G., and Benzon, B.: Sur l'importance du zinc dans l'alimentation des animaux: Expériences sur la souris, *Comp. rend. Acad. d. sc.* **175**: 289-292, 1922. McHargue, J. S.: Further Evidence That Small Quantities of Copper, Manganese and Zinc Are Factors in the Metabolism of Animals, *Am. J. Physiol.* **77**: 245-255 (July) 1926. Hubbell, Rebecca E., and Mendel, L. B.: Zinc and Normal Nutrition, *J. Biol. Chem.* **75**: 567-586, 1927. Bertrand, G., and Bhattacharjee, R. C.: L'action combinée du zinc et des vitamines dans l'alimentation des animaux, *Comp. rend. Acad. d. sc.* **198**: 1823-1827 (May 23) 1934.

102. Todd, W. R.; Elvehjem, C. A., and Hart, E. B.: Zinc in the Nutrition of the Rat, *Am. J. Physiol.* **107**: 146-156 (Jan.) 1934.

tive diets the Wisconsin investigators¹⁰³ have produced greater differences in growth and have again observed changes in the fur. The need for zinc in rats has been confirmed,¹⁰⁴ and it has been shown that mice require the element.¹⁰⁵ Microscopic study in instances of the deficiency¹⁰⁶ revealed extreme parakeratosis of the esophagus with a thick layer of partially keratinized cells; the skin showed hyperkeratinization, thickening of the epidermis and loss of hair follicles with persistence of the sebaceous glands. Several animals showed corneal vascularization similar to that described in riboflavin deficiency.¹⁰⁷

The physiologic role of zinc has been under intensive investigation. Scott and Fisher¹⁰⁸ have reported its occurrence in insulin; this close association has been confirmed.¹⁰⁹ Zinc⁶⁸ (as well as some other elements¹¹⁰) reduces the severity of insulin hypoglycemia while prolonging it. Scott and Fisher¹¹¹ found that the average zinc content of the pancreas of diabetic patients was only half that of the nondiabetic, while the insulin content was only one fourth. However, a recent report¹¹² indicates that on a fat free weight basis the zinc content of the pancreases of the diabetic and the nondiabetic is the same.

103. Stirn, F. E.; Elvehjem, C. A., and Hart, E. B.: The Indispensability of Zinc in Nutrition of the Rat, *J. Biol. Chem.* **109**: 347-359 (April) 1935. Hove, E.; Elvehjem, C. A., and Hart, E. B.: The Physiology of Zinc in the Nutrition of the Rat;¹²³ Further Studies on Zinc Deficiency in Rats, *Am. J. Physiol.* **124**: 750-758 (Dec.) 1938.

104. Day, H. G., and McCollum, E. V.: Effects of Acute Dietary Zinc Deficiency in the Rat, *Proc. Soc. Exper. Biol. & Med.* **45**: 282-284, 1940.

105. Day, H. G.: The Effects of Zinc Deficiency in the Mouse, *Federation Proc.* **1**: 188-189 (March) 1942.

106. Follis, R. H., Jr., and Day, H. G.: Histological Studies of the Tissues of Rats Fed a Diet Extremely Low in Zinc, *J. Nutrition* **22**: 223-237 (Sept.) 1941.

107. Bessey, O. A., and Wolbach, S. B.: Vascularization of the Cornea of the Rat in Riboflavin Deficiency with a Note on Corneal Vascularization in Vitamin A deficiency, *J. Exper. Med.* **69**: 1-12 (Jan.) 1939.

108. Scott, D. A.: Crystalline Insulin, *Biochem. J.* **28**: 1592-1602, 1934. Scott, D. A., and Fisher, A. M.: Crystalline Insulin, *ibid.* **29**: 1048-1054, 1935.

109. Cohn, E. J.; Ferry, J. D.; Livingood, J. J., and Blanchard, M. H.: The Solubility and Dielectric Properties of Insulin and Its Crystallization with Radioactive Zinc, *Science* **90**: 183-185 (Aug. 25) 1939.

110. Bischoff, F., and Jemtegaard, L. M.: Divided Dosage of Insulin, *Am. J. Physiol.* **110**: 149-152 (May) 1937. Blatherwick, N. R.; Ewing, Mary E., and Bradshaw, Phoebe J.: Some Effects of Zinc and Iron Salts on the Hypoglycemic Action of Insulin in Rats, *Am. J. Physiol.* **121**: 44-48 (Jan.) 1938. Scott and Fisher.⁶⁸

111. Scott, D. A., and Fisher, A. M.: The Insulin and the Zinc Content of Normal and Diabetic Pancreas, *J. Clin. Investigation* **17**: 725-728 (Nov.) 1938.

112. Eisenbrand, J., and Sienz, M.: Ueber den Zinkgehalt von menschlichen Pankreasdrüsen, *Ztschr. f. physiol. Chem.* **268**: 1-35 (March) 1941.

Carbonic anhydrase, the enzyme which accelerates the reaction $\text{H}_2\text{CO}_3 \rightleftharpoons \text{CO}_2 + \text{H}_2\text{O}$,¹¹³ appears to be a zinc-protein compound,¹¹⁴ although reports vary as to the zinc content.¹¹⁵ It has been found in the blood, gastric mucosa,¹¹⁶ pancreas¹¹⁷ and renal cortex;¹¹⁸ apparently all of the zinc in the erythrocytes is in this enzyme,¹¹⁹ which, incidentally, is inhibited by sulfanilamide.¹²⁰ The enzyme uricase may also contain zinc.¹²¹

In view of these findings, it is interesting to note the observations on the physiology of zinc deficient animals. Thus far there have been found no disorder of carbohydrate metabolism,¹²² no significant decrease in the carbonic anhydrase activity¹²³ and no decrease in the concentration of uricase.¹²⁴ On the other hand, the deficient rats showed a persistent rise in plasma uric acid,¹²⁴ a definite delay in intestinal absorption, particularly of nitrogenous products,¹²² associated with decreases in pancreatic tryptic activity (nonspecific) and intestinal phosphatase activity.¹²⁵ Catalase activity in liver and kidney is decreased in zinc deficient mice.¹⁰⁵

If its concentration in many tissues and foods is taken as the criterion, zinc should not be classified as a "trace" element if iron is not, since it occurs in amounts approx-

113. Roughton, F. J. W.: Recent Work on the Carbon Dioxide Transport by the Blood, *Physiol. Rev.* **15**: 241-296 (April) 1935.

114. Keilin, D., and Mann, T.: Carbonic Anhydrase, *Nature* **144**: 442-443 (Sept. 2) 1939.

115. Hove, E.; Elvehjem, C. A., and Hart, E. B.: The Relation of Zinc to Carbonic Anhydrase, *J. Biol. Chem.* **136**: 425-434 (Nov.) 1940. Scott, D. A., and Mendive, J. R.: Chemical Observations on Carbonic Anhydrase, *ibid.* **140**: 445-451 (Aug.) 1941. Keilin and Mann.¹¹⁴

116. Davenport, H. W.: Gastric Carbonic Anhydrase, *J. Physiol.* **97**: 32-43 (Nov.) 1939.

117. van Goor, H.: La répartition de l'anhydrase carbonique dans l'organisme des animaux, *Arch. internat. physiol.* **45**: 491-509 (Dec.) 1937. Tucker, Helen F., and Ball, E. G.: The Activity of Carbonic Anhydrase in Relation to the Secretion and Composition of Pancreatic Juice, *J. Biol. Chem.* **139**: 71-80 (May) 1941.

118. Davenport, H. W., and Wilhelmi, A. E.: Renal Carbonic Anhydrase, *Proc. Soc. Exper. Biol. & Med.* **48**: 53-56 (Oct.) 1941.

119. Keilin and Mann.¹¹⁴ Hove, Elvehjem and Hart.¹¹⁵

120. Mann, T., and Keilin, D.: Sulfanilamide as a Specific Inhibitor of Carbonic Anhydrase, *Nature* **146**: 164-165 (Aug. 3) 1940.

121. Holmberg, C. G.: Uricase Purification and Properties, *Biochem. J.* **33**: 1901-1906, 1939. Davidson, J. N.: The Purification of Uricase. 2. Some Properties of Purified Uricase, *ibid.* **36**: 252-258 (Feb.) 1942.

122. Hove, E.; Elvehjem, C. A., and Hart, E. B.: The Physiology of Zinc in the Nutrition of the Rat, *Am. J. Physiol.* **119**: 768-775 (Aug.) 1937.

123. Hove, Elvehjem and Hart.¹¹⁵ Day and McCollum.¹⁰⁴

124. Wachtel, L. W.; Hove, E.; Elvehjem, C. A., and Hart, E. B.: Blood Uric Acid and Liver Uricase of Zinc Deficient Rats on Various Diets, *J. Biol. Chem.* **138**: 361-368 (March) 1941.

125. Hove, Elias; Elvehjem, C. A., and Hart, E. B.: The Effect of Zinc on Alkaline Phosphatases, *J. Biol. Chem.* **134**: 425-442 (June) 1940.

imating those of iron;¹²⁶ in some cases zinc occurs in greater concentrations, milk, for example, containing 3 to 4 mg. per liter. The average daily diet contains 12 to 20 mg. of zinc, almost all being excreted in the urine. For the present there is no information on the zinc requirement of man. Several balance studies, one on children of preschool age¹²⁷ and the other on children 8 to 12 years old,¹²⁸ have shown zinc retention, indicating possible requirements. Scoular¹²⁷ tentatively recommends 0.307 mg. of zinc daily per kilogram of body weight for the preschool age child.

FLUORINE

The consideration of fluorine in any discussion of trace elements is pertinent for at least two reasons: first, because of the undesirable effects associated with widespread chronic fluorine intoxication, and, second, because of the recent interest in the effect of fluorine on the incidence and severity of dental caries.

Fluorine associated with various minerals is widely distributed in nature, especially in areas rich in phosphates, aluminum and volcanic ash. It is present normally in very small amounts in plant and animal tissues. McClure¹²⁹ has collected data on the fluorine content of foods and vegetables.

Water passing through fluorine rich mineral deposits becomes contaminated with the element, and consumption of this water during the period of tooth formation, particularly of the permanent teeth, results in a disease known as chronic endemic dental fluorosis, commonly called mottled enamel. Recognition that the disease is water borne came¹⁸⁰ in 1916, but it was not until

126. Lutz, R. E.: The Normal Occurrence of Zinc in Biological Materials: A Review of the Literature and a Study of the Normal Distribution of Zinc in the Rat, Cat and Man, *J. Indust. Hyg.* **8**: 177-207, 1926. Eggleton, W. G. E.: The Zinc Content of Epidermal Structures in Beriberi, *Biochem. J.* **33**: 403-406 (April) 1939.

127. Scoular, Florence I.: A Quantitative Study, by Means of Spectrographic Analysis, of Zinc in Nutrition, *J. Nutrition* **17**: 103-113 (Feb.) 1939.

128. Stern, A.; Naldar, Margaret, and Macy, Icie G.: Zinc Retention in Childhood, *J. Nutrition* **21**: 8, 1941, *Proc. Macy, Icie G.: Nutrition and Chemical Growth in Childhood*, vol. 1, Evaluation, Springfield, Ill., Charles C. Thomas, 1942.

129. McClure, F. J.: Fluorides in Food and Drinking Water, *Bulletin* **172**, Nat. Inst. Health, 1939.

130. McKay, F. S., in collaboration with Black, G. V.: An Investigation of Mottled Teeth, *Dent. Cosmos* **58**: 477-484 (May), 627-644 (June) 1916.

1931 that three independent investigations¹³¹ implicated fluoride as the causative agent. Epidemiologic studies and animal experimentation fully support this view. Surveys of populations¹³² indicate an orderly uniformity in the group response to the fluoride concentration of the communal water supply with regard both to the incidence and to the percentage distribution of the severity of the mottled enamel, particularly the latter, as shown in the table. Amounts of fluoride not exceeding one part per million of water are not considered of public health significance.¹³²

Relation of Fluoride Concentration to Incidence of Mottled Enamel in Children

(Nichols, M. S.,¹³¹ from data of Dean and Elvove.¹³²)

City and State	Fluoride Content in Parts per Million of Drinking Water	Composite of 9, 10 and 11 Year Old Children	
		Number of Children Examined	Incidence per 100 Children
Junction City, Kan... ..	0.7	115	1.7
East Moline, Ill..... ..	1.5	110	24.5
Webster City, Iowa..... ..	1.6	72	26.4
Olovia, N. M..... ..	2.2	138	71.0
Plainview, Texas.	2.9	77	87.0
Amarillo, Texas..... ..	3.9	229	89.5
Conway, S. O..... ..	4.0	59	88.1
Lubbock, Texas... ..	4.4	164	97.6

The widespread occurrence of mottled enamel in the United States is indicated in figure 1. Its distribution is worldwide.

As fluorine acts during the period of calcification, the teeth of the affected child erupt, showing characteristic signs. Instead of having the normal smooth, lustrous, translucent appearance, the teeth have dull chalky white patches distributed over the surface, and in some cases the whole tooth surface may present a dead white unglazed appearance. In addition there

131. Churchill, H. V.: Occurrence of Fluorides in Some Waters of the United States, *Indust. & Engin. Chem.* **23**:996-998 (Sept.) 1931. Smith, Margaret C.; Lantz, E. M., and Smith, H. V.: The Cause of Mottled Enamel, a Defect of Human Teeth, *Tech. Bull.* 32, Univ. Arizona Agr. Exper. Stat., June 1931, pp. 253-282. Velu, H.: Dystrophie dentaire des mammifères des zones phosphatées (darmous) et fluorose chronique, *Comp. rend. Soc. de biol.* **108**:750-752 (Nov. 21) 1931.

132. Dean, H. T., and Elvove, E.: Further Studies on the Minimal Threshold of Chronic Endemic Fluorosis, *Pub. Health Rep.* **52**:1249-1264 (Sept. 10) 1937.

may be discrete or confluent pitting of the enamel. The affected teeth often take on a characteristic brown stain, the frequency of occurrence increasing with age. Mottled enamel is a permanent disfigurement (figs. 2, 3, 4 and 5). The microscopic appearance is that of a hypoplasia of the enamel and dentin. There is a failure in the development of the cementing interprismatic substance of the enamel¹³³ with incomplete calcification of the enamel rods¹³⁴ and of the dentin.¹³⁵ Pitting is

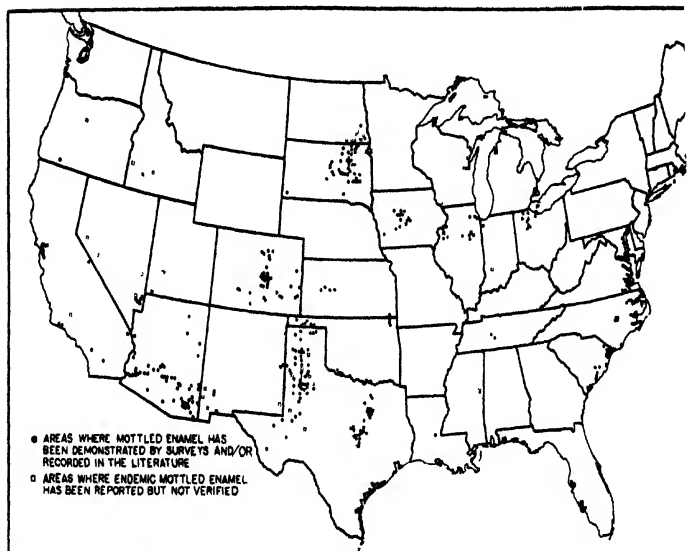


Fig. 1.—Distribution of mottled enamel in the United States. In August 1938 there were about three hundred and seventy-five known areas divided among twenty-six states where this condition occurred in varying degrees of severity (Dean, H. T., and McKay, F. S.: *Am. J. Pub. Health* 29: 490 [June] 1939).

the result of the breaking off of the end of the enamel prisms.

133. Black, G. V., in collaboration with McKay, F. S.: Mottled Teeth: An Endemic Developmental Imperfection of the Teeth, Heretofore Unknown in the Literature of Dentistry, *Dent. Cosmos* 58: 129-156 (Feb.) 1916.

134. Williams, J. L.: Mottled Enamel and Other Studies of Normal and Pathological Conditions of This Tissue, *J. Dent. Res.* 5: 117-195, (Sept.) 1923.

135. Beust, T. B.: A Contribution to the Etiology of Mottled Enamel, *J. Am. Dent. A.* 12: 1059-1066 (Sept.) 1925. Ainsworth, N. J.: Mottled Teeth, *Brit. Dent. J.* 55: 233-250, 274-276 (Sept.) 1933.

The solution to the problem lies in the reduction of the fluoride intake by a change in the community water supply,¹³⁶ by dilution of high fluoride waters or by treatment of the water to remove the fluorides.¹³⁷ Various aspects of endemic dental fluorosis have been reviewed in a number of recent papers.¹³⁸

Chronic fluorine poisoning may occur through exposure to dusts or fumes of fluoride containing minerals used in industrial processes. Roholm¹³⁹ in his monograph reviews the literature and discusses the poisoning of workers in Copenhagen factories where cryolite (Na_3AlF_6) was used in the production of aluminum. Gastric, intestinal, cardiac and respiratory disturbances were prominent, and osteosclerosis was the outstanding feature. All the bony system was affected eventually,



Fig. 2.—Mottled enamel (endemic dental fluorosis) of mild degree. This illustration and figure 5 are from Dean, H. T., and McKay, F. S.: *Am. J. Public Health* **29**: 590 (June) 1939, and figures 3 and 4 from Dean, H. T.; McKay, F. S., and Elvove, Elias: *Pub. Health Rep.* **53**: 1736 (Sept. 30) 1938, through the courtesy of Dr. Dean of the U. S. Public Health Service.

but the vertebral column and pelvis were affected first and most severely. Greenwood¹⁴⁰ in his comprehensive

136. Dean, H. T.: Chronic Endemic Dental Fluorosis (Mottled Enamel), *J. A. M. A.* **107**: 1269-1272 (Oct. 17) 1936. Dean, H. T., and McKay, F. S.: Production of Mottled Enamel Halted by Change in the Common Water Supply, *Am. J. Pub. Health* **29**: 590-596 (June) 1939.

137. Nichols, M. S.: Occurrence, Pathological Aspects and Treatment of Fluoride Waters, *Am. J. Pub. Health* **29**: 991-998 (Sept.) 1939.

138. Dean, H. T.: Fluorine, Mottled Enamel and Dental Caries, *J. Pediat.* **16**: 782-794 (June) 1940; Chronic Endemic Dental Fluorosis (Mottled Enamel).¹³⁹ Hawkins, J. W., and Gordon, J. E.: Epidemiological Aspects of Mottled Enamel, *Am. J. M. Sc.* **199**: 431-446 (March) 1940. Nichols.¹³⁷ Dean and McKay.¹³⁶

139. Roholm, K.: *Fluorine Intoxication*, London, H. K. Lewis Ltd., 1937.

140. Greenwood, D. A.: Fluoride Intoxication, *Physiol. Rev.* **20**: 582-616 (Oct.) 1940.

review of the recent literature also discusses acute and chronic fluoride poisoning.

Another possible source of chronic poisoning may be the use of fluorine containing insecticides used in spraying fruits and vegetables. This has necessitated a federal legal tolerance on such spray residues of $\frac{2}{100}$ grain of fluorine per pound of food, which is equivalent to about 2.9 parts per million.

McCollum and his co-workers¹⁴¹ and Schulz and Lamb¹⁴² first showed the detrimental effects of the inclusion of fluoride in the diet of experimental animals. Their observations¹⁴¹ on the bleaching and fragility



Fig 3.—Mottled enamel of moderate degree. Note the whiteness, pigmentation, pitting and lack of luster particularly noticeable in this illustration and in figure 4

of the bones and teeth and of the overgrowth of the maxillary incisors following excessive erosion of the opposing mandibular incisors¹⁴³ have been confirmed by numerous investigators who have added to our knowledge. The use of natural phosphates or superphosphates with high fluoride content as mineral supplements to farm animals has frequently resulted in chronic fluoride poisoning. Stunting of growth, ema-

141. McCollum, E. V., Simmonds, Nina; Becker, J. Ernestine, and Bunting, R. W. The Effect of Additions of Fluorine to the Diet of the Rat on the Quality of the Teeth, *J. Biol. Chem.* **63**: 553-562 (April) 1925.

142. Schulz, J. A., and Lamb, A. R. The Effect of Fluorine as Sodium Fluoride on the Growth and Reproduction of Albino Rats, *Science* **61**: 93-94 (Jan. 23) 1925.

143. McCollum, Simmonds, Becker and Bunting¹⁴¹ Schulz and Lamb¹⁴²

ciation, lameness due to bone abnormality and fragility, and tooth changes similar to those of human dental fluorosis have been described.¹⁴⁴

Additional evidence for the action of fluorine as a modifier of calcium and phosphorus metabolism is the observation¹⁴⁵ that fluoride decreases the severity of rickets in rats, prolongs the life of rachitic rats¹⁴⁶ and causes an unorganized calcification when vitamin D is given.¹⁴⁵ When administered together with vitamin D to rachitic rats, it inhibits the healing process. Fluoride given to the normal mother causes delay and some disorganization of calcification of the bones of suckling rats.¹⁴⁷ Greenwood¹⁴⁰ cites recent reports that patho-

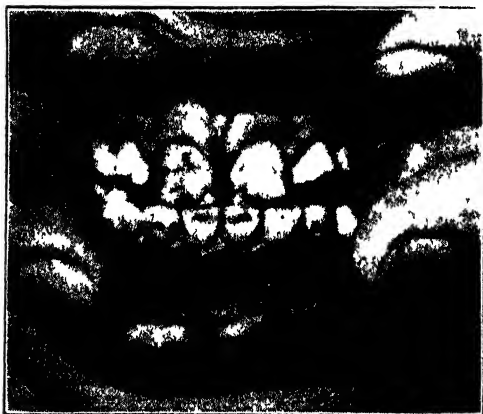


Fig. 4.—Mottled enamel of severe degree. The pigmentation occurs after tooth eruption and increases with age.

logic bone changes occur in people living in endemic mottled areas for long periods of time. However, in a recent radiologic study¹⁴⁸ of persons in two Illinois

144. Peirce, A. W.: Chronic Fluorine Intoxication in Domestic Animals, *Nutrition Abstr. & Rev.* **9**: 253-261 (Oct.) 1939. Bosworth, T. J., Green, H. H., and Murray, M. M.: Discussion on Fluorosis in Man and Animals, *Proc. Roy. Soc. Med.* **34**: 391-396 (May) 1941.

145. Morgareidge, K., and Finn, S. B.: Effect of Fluorine on the Activity of Vitamin D in Rachitic Rats, *J. Nutrition* **30**: 75-84 (July) 1940.

146. Finn, B. B., and Kramer, M.: Effect of Fluorine on Life Span of Rachitic Rats, *Proc. Soc. Exper. Biol. & Med.* **45**: 843-845 (Dec.) 1940.

147. Glock, G. E.: Glycogen and Calcification, *J. Physiol.* **98**: 1-11 (March) 1940.

148. Hodges, P. C.; Fareed, O. J.; Ruggy, George, and Chudnof, J. S.: Skeletal Sclerosis in Chronic Sodium Fluoride Poisoning, *J. A. M. A.* **117**: 1938 (Dec. 6) 1941.

communities, where the water supplies contained 1.5 to 3 parts per million of fluoride and where dental fluorosis was widespread, no demonstrable skeletal sclerosis occurred even though the water was taken for long periods. Smith¹⁴⁹ was unable to find any bony changes in children with mottled teeth and suggested that teeth are much more sensitive to fluoride than the bony skeleton.

Fluoride is known as an enzyme poison, specifically inhibiting the formation of phosphopyruvate from phosphoglycerate. The reports in the literature on its effect on phosphatases *in vivo* are conflicting.¹⁵⁰ *In vitro* experiments indicate an inhibition of phosphatases¹⁵¹ and esterases.¹⁵²

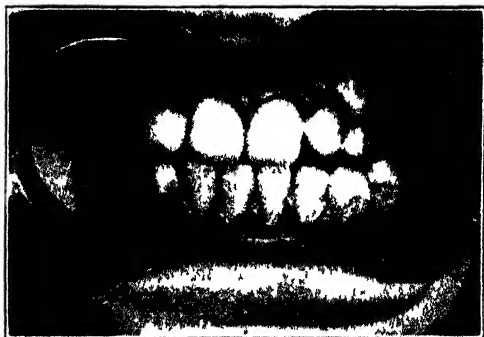


Fig. 5.—Normal enamel.

The synergistic action of thyroid and fluoride has been noted. Fluoride when given in conjunction with thyroid accentuates the effect on the basal metabolic rate produced by the thyroid, whereas the fluorine alone

149. Smith, Margaret C.: Fluorine Toxicosis: A Public Health Problem, *Am. J. Pub. Health* **25**: 696-702 (June) 1935.

150. Shortt, H. E.; McRobert, G. R.; Barnard, T. W., and Nayar, A. S. M.: Endemic Fluorosis in the Madras Presidency, *Indian J. M. Res.* **25**: 553-568 (Oct.) 1937. DeEds, Floyd: Factors in the Etiology of Mottled Enamel, *J. Am. Dent. A.* **28**: 1804-1814 (Nov.) 1941. Smith, Margaret C., and Lantz, Edith M.: The Effect of Fluorine on the Phosphatase Content of Plasma, Bones and Teeth of Albino Rats, *J. Biol. Chem.* **112**: 303-311 (Dec.) 1935. Phillips, Hart and Bohstedt.¹⁵⁰

151. Ochoa, S.: "Coupling" of Phosphorylation with Oxidation of Pyruvic Acid in Brain, *J. Biol. Chem.* **138**: 751-773 (April) 1941. Massart, L., and Dufait, R.: Fluoridhemmung und Metallaktivierung der Hefephosphatase, *Naturwissensch.* **27**: 806-807 (Dec. 1) 1939.

152. Loevenhart, A. S., and Peirce, G.: The Inhibiting Effect of Sodium Fluoride on the Action of Lipase, *J. Biol. Chem.* **2**: 397-413, 1908.

has no effect.¹⁵³ Fluoride enhances the toxicity of thyroid in chicks and vice versa.¹⁵⁴ Thyroid and thyrotropic hormone likewise enhance the bleaching of rat incisors by fluoride.¹⁵⁵

The fluoride content of cow's milk is only slightly affected by increasing the fluoride intake—the milk level remaining appreciably below toxic levels.¹⁵⁶ However, it is possible that women exposed to fluorides may be able to transmit enough fluoride in their milk to affect the developing teeth of the infant.¹⁵⁷ From the somewhat meager evidence¹⁵⁸ it would appear that food is relatively unimportant compared to water as a source of this element. The question has been presented^{158a} of the possible danger of chronic fluorine poisoning arising from the use of dicalcium phosphate as a dietary supplement during pregnancy and for infants and children.

Fluorine has become of even greater nutritional interest and importance since the discovery of Armstrong¹⁵⁹ and Armstrong and Brekhus¹⁶⁰ that the enamel of sound teeth contained more fluorine than that of carious teeth, their average values being 0.0111 and 0.0069 per cent respectively. This is the only element whose concentration has been found to differ between normal

153. Phillips, P. H.; English, H. E., and Hart, E. B.: The Influence of Sodium Fluoride on the Basal Metabolism of the Rat Under Several Experimental Conditions, *Am. J. Physiol.* **113**: 441-449 (Oct.) 1935.

154. Phillips, P. H.; English, H. E., and Hart, E. B.: The Augmentation of the Toxicity of Fluorosis in the Chick by Feeding Desiccated Thyroid, *J. Nutrition* **10**: 399-407 (Oct.) 1935.

155. Wilson, R. H., and DeEds, Floyd: Synergistic Action of Thyroid on Fluorine Toxicity, *Endocrinology* **26**: 851-856 (May) 1940. DeEds, Floyd; Wilson, R. H., and Cutting, W. C.: Thyrotropic Hormone and Fluorine Activity, *Endocrinology* **26**: 1053-1056 (June) 1940.

156. Phillips, P. H.; Hart, E. B., and Bohstedt, G.: The Influence of Fluorine Ingestion on the Nutritional Qualities of Milk, *J. Biol. Chem.* **105**: 123-134 (April) 1934. Smith, Margaret C.; Vavich, M., and Smith, H. V.: Fluorine Content of Milk as Affected by the Amount of Fluorine in the Drinking Water of the Cow, *J. Dent. Res.* **20**: 286-287 (June) 1941, *Proc.*

157. Brinch, O., and Roholm, K.: *Paradentium* **6**: 147, 1934, cited by Bosworth, Green and Murray.¹⁴⁴

158. Hart, E. B.; Phillips, P. H., and Bohstedt, G.: Relation of Soil Fertilization with Superphosphate and Rock Phosphate to Fluorine of Plants and Drainage Waters, *Am. J. Pub. Health* **24**: 936-940 (Sept.) 1934. Mackle, W.; Scott, E. W., and Treon, J.: Normal Urinary Fluoride Excretion and the Fluorine Content of Food and Water, *Am. J. Hyg.* **29**: 139-145 (sec. A., May) 1939. McClure.¹²⁹

158a. DeEds, F.: The Toxicity of Fluorine in Dicalcium Phosphate, *Am. J. M. Sc.* **203**: 687-692 (May) 1942.

159. Armstrong, W. D.: Fluorine Content of Enamel and Dentin of Sound and Carious Teeth, *Proc. Am. Soc. Biol. Chem., J. Biol. Chem.* **119**: v, 1937.

160. Armstrong, W. D., and Brekhus, P. J.: Possible Relationship Between the Fluorine Content of Enamel and Resistance to Dental Caries, *J. Dent. Res.* **17**: 393-399 (Oct.) 1938.

and carious teeth, and the suggestion was made that the increased fluorine content might play a role in the resistance to caries.

Numerous papers have since appeared of a chemical, clinical and experimental nature with supporting evidence for a relationship between fluorine and the incidence of dental caries. It is interesting to note that before the finding of Armstrong and Brekhuis there were many observations in the literature¹⁶¹ pointing out a decreased severity of caries in areas of endemic dental fluorosis.

Dean and his co-workers¹⁶² have published a valuable series of papers concerned with human epidemiologic studies. They indicate an inverse relationship between the fluoride concentration of the water supply and the incidence of dental caries in children. It is significant that in communities with a water supply containing fluorides in concentration but slightly above the minimal threshold of endemic dental fluorosis (1.0 part per million) and where the incidence of mottled enamel was low, the dental caries experience was much less than in communities using fluoride free water.¹⁶³ Earlier work¹⁶² had shown the inverse relationship between endemic dental fluorosis and dental caries, but the later results indicate that the limited immunity to dental caries is not dependent on the presence of macroscopic mottled enamel. The results at Bauxite, Ark.,¹⁶⁴ indicate that exposure to high fluoride water

161. Bunting, R. W.; Crowley, M.; Hard, D. H., and Keller, M. Further Studies on Relation of *B. Acidophilus* to Dental Caries, *Dent. Cosmos* **70**:1002-1009 (Oct.) 1928. McKay, F. S.: Establishment of Definite Relation Between Enamel That Is Defective in Structure, as Mottled Enamel, and Its Liability to Decay, *ibid.* **71**:747-755 (Aug.) 1929. Arnim, S. S.; Aberle, S. D., and Pitney, E. H.: A Study of Dental Changes in a Group of Pueblo Indian Children, *J. Am. Dent. A.* **24**:478-480 (March) 1937. Masaki, T.; Gakuho Shikwa **26**:17, 1931, cited by Dean: Fluorine, Mottled Enamel and Dental Caries.¹⁵⁹ Ainsworth.¹⁴⁵ Black.¹⁵⁸

162. Dean, H. T.: Endemic Fluorosis and Its Relation to Dental Caries, *Pub. Health Rep.* **53**:1443-1452 (Aug. 19) 1938. Dean, H. T.; Jay, P.; Arnold, F. A., Jr.; McClure, F., and Elvove, E.: Domestic Water and Dental Caries, Including Certain Epidemiological Aspects of Oral *L. Acidophilus*, *ibid.* **54**:862-888 (May 26) 1939. Dean, Jay, Arnold and Elvove, footnotes 163 and 164.

163. Dean, H. T.; Jay, P.; Arnold, F. A., Jr., and Elvove, E.: Domestic Water and Dental Caries: II. A Study of 2,832 White Children, Aged 12 to 14 Years, of Eight Suburban Chicago Communities, Including *Lactobacillus Acidophilus* Studies of 1,761 Children, *Pub. Health Rep.* **56**:761-792 (April 11) 1941.

164. Dean, H. T.; Jay, P.; Arnold, F. A., Jr., and Elvove, E.: A Dental Caries Study, Including *L. Acidophilus* Estimations of a Population Severely Affected by Mottled Enamel and Which for the Past Twelve Years Has Used a Fluoride Free Water, *Pub. Health Rep.* **56**:365-381 (Feb. 28) 1941.

for only the first several years of life resulted in increased resistance to caries for at least several years after a change to a low fluoride water supply. In all the studies the salivary *Bacillus acidophilus* counts reflected the dental caries rate. Evidence that the problem needs further study is given in the recent report^{164a} of a study of school children exposed for two years to a domestic water which was increased in fluoride content from .1 to 0.7 parts per million. The dental caries experience rate and the *L. acidophilus* counts were similar to those in communities with fluoride-free water.

Recent investigations with rats show that fluorides can greatly inhibit induced dental caries when administered either during tooth development¹⁶⁵ or after formation of the teeth.¹⁶⁶ The mechanism by which fluoride acts is not completely established, but it appears to be by one or both of the following: (a) by the fluoride entering the tooth structure and giving it caries resistant properties or (b) by inhibiting bacterial action on food particles and on the tooth. There is evidence for both views.

Fluorides in minute amounts limit acid production by mouth bacteria, as do fluorosed and fluorine treated enamel and dentin; in larger amounts growth is inhibited.¹⁶⁷ In vitro and in vivo acquisition of fluorine

164a. Arnold, F. A.; Dean, H. T., and Elvove, E.: Domestic Water and Dental Caries. IV. Effect of Increasing the Fluoride Content of a Common Water Supply on the *Lactobacillus Acidophilus* Counts of the Saliva, Pub. Health Rep. 57: 773-780 (May 22) 1942.

165. Cox, G. J.; Matuschak, Margaret C.; Dixon, Sara F.; Dodds, Mary L., and Walker, W. E.: Fluorine and Its Relation to Dental Caries, J. Dent. Res. 18: 481-490 (Dec.) 1939.

166. Miller, B. F.: Inhibition of Experimental Dental Caries in the Rat by Fluoride and Iodoacetic Acid, Proc. Soc. Exper. Biol. & Med. 39: 389-393 (Nov.) 1938. Hodge, H. C., and Finn, S. B.: Reduction in Experimental Rat Caries by Fluorine, *ibid.* 42: 318-320 (Oct.) 1939. Sognnaes, R. F.: Effect of Local and Systemic Fluorine Administration on Experimental Rat Caries, J. Dent. Res. 19: 287 (June) 1940, Proc. Cheyne, V. D.: Inhibition of Experimental Dental Caries by Fluorine in the Absence of Saliva, Proc. Soc. Exper. Biol. & Med. 43: 58-61 (Jan.) 1940; Study of the Mechanism of Inhibition of Dental Caries by Fluorine, J. Dent. Res. 19: 280-281 (June) 1940, Proc. McClure, F. J., and Arnold, F. A., Jr.: Observations on Induced Dental Caries in Rats: Reduction by Fluorides and Iodoacetic Acid, *ibid.* 50: 97-105 (April) 1941. Finn, S. B., and Hodge, H. C.: Reduction in Experimental Caries by Fluorine, J. Nutrition 23: 255-266 (Sept.) 1941. McClure, F. J.: Effect of Fluoride on Rat Caries and on Composition of Rat's Teeth, *ibid.* 23: 391-398 (Oct.) 1941.

167. Bibby, B. G., and Van Kesteren, M.: The Effect of Fluorine on Mouth Bacteria, J. Dent. Res. 19: 391-402 (Aug.) 1940. Harrison, R. W.: Bacterial Flora in Experimental Dental Caries of the Rat, Proc. Soc. Exper. Biol. & Med. 39: 459-461 (Dec.) 1938.

by teeth has been studied,¹⁶⁸ it has been found that enamel and dentin can acquire fluoride and that treated samples show reduced solubility,¹⁶⁹ although apparently the amounts of fluoride present in slightly fluorosed teeth are too small to alter their acid solubility. Arnold and McClure¹⁷⁰ have found that subcutaneous injection of fluoride as contrasted to oral administration produced no significant reduction in induced dental caries of rats, although the fluoride content of the teeth increased, they believe that these results show that if fluoride acts by affecting structure it must be introduced during the period of tooth development.

Fluorine's concomitant effect of mottling enamel even in minute amounts unfortunately means that for the present, at least, its use as an inhibitor of human dental caries is most decidedly in the experimental stage. It remains to be seen whether topical application of fluoride or its intake by persons whose permanent teeth have already formed are effective and safe means of inhibiting dental caries. One recent preliminary report on topical application to a small number of cases over a period of only one year is optimistic.^{170a}

There is no evidence from the investigations with fluorine-low diets¹⁷¹ that this element is essential. However, more refined nutritional experiments or the elucidation of its role in tooth and bone structure may show that it is necessary.

SELENIUM

Selenium poisoning has gained prominence as a problem in livestock nutrition and as a possible health

168. Volker, J. F.; Hodge, H. C.; Wilson, H. J., and Van Voorhis, S. N.: The Adsorption of Fluorides by Enamel, Dentin, Bone and Hydroxyapatite as Shown by the Radioactive Isotope, *J. Biol. Chem.* **134**: 543-548 (July) 1940. Perry, Mabel W., and Armstrong, W. D.: On the Manner of Acquisition of Fluorine by Mature Teeth, *J. Nutrition* **21**: 35-44 (Jan.) 1941. McClure,¹⁶⁹ Norvold, R. W.; Inglis, J. H., and Armstrong, W. D.: External Acquisition of Fluorine by Enamel, *J. Dent. Res.* **20**: 232-233 (June) 1941, Proc. Volker,¹⁶⁹ McClure, F. J.: Fluorine Acquired by Mature Dog's Teeth, *Science* **95**: 256 (March 6) 1942.

169. Volker, J. F.: Effect of Fluorine on Solubility of Enamel and Dentin, *Proc. Soc. Exper. Biol. & Med.* **42**: 725-727 (Dec.) 1939; Solubility of Fluorosed Enamel and Dentin, *ibid.* **43**: 643-645 (April) 1940.

170. Arnold, F. A., Jr., and McClure, F. J.: Observations on Induced Dental Caries in Rats: II. The Effect of Subcutaneous Injection of Fluoride, *J. Dent. Res.* **20**: 457-463 (Oct) 1941.

170a. Cheyne, V. D.: *J. Am. Dent. A.* **29**: 804-807 (May) 1942.

171. Sharpless, G. R., and McCollum, E. V.: Is Fluorine an Indispensable Element in the Diet? *J. Nutrition* **6**: 163-178 (March) 1933. Evans, R. J., and Phillips, P. H.: A New Low Fluorine Diet and Its Effect on the Rat, *ibid.* **13**: 353-360 (Oct.) 1939.

hazard to man since 1933, when selenium was found¹⁷² in samples of wheat which had previously been shown to be toxic to livestock and to laboratory animals.¹⁷³ The ingestion of selenium bearing vegetation has thus been thought to be concerned with the pathologic conditions of farm animals known as "alkali disease" and "blind staggers."¹⁷⁴ Plants growing in seleniferous areas often contain high concentrations of the element in some organic form and presumably in the protein fraction.¹⁷⁵ The affected localities are limited in size but widely scattered throughout the Great Plains of the western United States.¹⁷⁶

Selenium poisoning results in stunting of growth, emaciation, loss of hair, decreased reproductive power, atrophy and cirrhosis of the liver, gastric damage and anemia.¹⁷⁷ Cattle, hogs and horses develop erosion of the bones, abnormalities of the hooves, and atrophy of the heart in the chronic form of the poisoning ("alkali disease").¹⁷⁷ The eggs of poisoned poultry have a low hatchability because of the abnormal development of the embryos into monstrosities.¹⁷⁸ Experiments with various species have demonstrated¹⁷⁹ that daily ingestion of selenium in amounts as low as 0.2 mg. per kilogram of weight causes minor symptoms and that doses in excess of 1 mg. per kilogram daily are dangerously toxic. The natural plant toxicant is less toxic than the inorganic salts but the symptoms are the same. It is noteworthy that within certain limits the toxicity of plant and inorganic selenium is determined by the

172. Robinson, W. O.: Determination of Selenium in Wheat and Soils, J. A. Off. Agr. Chem. **16**: 423-424, 1933.

173. Franke, K. W.: A New Toxicant Occurring Naturally in Certain Samples of Plant Foodstuffs. I. Results Obtained in Preliminary Feeding Trials, J. Nutrition **8**: 597-608 (Nov.) 1934. Moxon.¹⁷⁴

174. Moxon, A. L.: Alkali Disease or Selenium Poisoning, Bull. 311, South Dakota Agr. Exper. Sta., May 1937, pp. 1-91. Moxon includes in this detailed review an account of Franke's work beginning in 1929.

175. Franke, K. W., and Painter, E. P.: Selenium in Proteins from Toxic Foodstuffs: 1. Remarks on the Occurrence and Nature of the Selenium Present in a Number of Foodstuffs or Their Derived Products, Cereal Chem. **13**: 67-70 (Jan.) 1936. Jones, D. B.; Horn, M. J., and Gersdorff, C. E. F.: The Selenium and Cystine Contents of Some Partial Hydrolysis Products of Gluten from Toxic Wheat, *ibid.* **14**: 130-134 (Jan.) 1937.

176. Trelease, S. F.: Bad Earth, Scient. Month. **54**: 13-28 (Jan.) 1942.

177. Moxon.¹⁷⁴ Smith, Lillie, Stohlman and Westfall.¹⁷⁹

178. Franke, K. W., and Tully, W. C.: A New Toxicant Occurring Naturally in Certain Samples of Plant Foodstuffs: V. Low Hatchability Due to Deformities in Chicks, Poultry Sc. **14**: 273-279, 1935. Franke, K. W.; Moxon, A. L.; Poley, W. E., and Tully, W. C.: Monstrosities Produced by the Injection of Selenium Salts into Hen's Eggs, Anat. Rec. **65**: 15-22 (April) 1936.

179. Smith, M. I.; Lillie, R. D.; Stohlman, E. F., and Westfall, B. B.: Studies in Chronic Selenosis, Bull. 174, Nat. Inst. Health, 1940. Moxon.¹⁷⁴

protein-selenium ratio in the diet rather than by the selenium intake.¹⁸⁰ Selenium compounds inhibit cellular respiration probably by poisoning enzymes, such as succinodehydrogenase, which are dependent on sulphydryl groups for activity.¹⁸¹

Persons living in rural areas where selenium is endemic absorb selenium in sufficient amounts to excrete it in concentrations¹⁸² much greater than those found in nonseleniferous areas.¹⁸³ Analysis for selenium revealed its widespread occurrence in animal as well as plant foodstuffs from seleniferous localities. There is no definite clinical evidence of human selenium intoxication in these areas, but there is suggestive evidence that man is not immune.¹⁸² The seriousness of selenium poisoning in these populations is undoubtedly reduced by the fact that much of the flour and vegetables consumed come from nonseleniferous regions.¹⁸⁴

BORON

Although boron is known to be essential for plants, there is as yet no experimental evidence that it is necessary for animals. It appears to exist normally in small amounts in animals,¹⁸⁵ in milk¹⁸⁶ and in eggs.¹⁸⁷

180. Smith, M. I.: The Influence of Diet on the Chronic Toxicity of Selenium, *Pub. Health Rep.* **54**: 1441-1453 (Aug. 4) 1939; Lewis, H. B.; Schultz, J., and Gortner, R. A., Jr.: Dietary Protein and the Toxicity of Sodium Selenite in the White Rat, *J. Pharmacol. & Exper. Therap.* **68**: 292-299 (Feb.) 1940.

181. Wright, C. I.: The Effect of Sodium Selenite and Selenate on the Oxygen Consumption of Mammalian Tissues, *Pub. Health Rep.* **53**: 1825-1836 (Oct. 14) 1938; Effect of Selenium on Urease and Arginase, *J. Pharmacol. & Exper. Therap.* **68**: 220-230 (Feb.) 1940.

182. Smith, M. T.; Franke, K. W., and Westfall, B. B.: Selenium Problem in Relation to Public Health: Preliminary Survey to Determine Possibility of Selenium Intoxication in the Rural Population Living on Seleniferous Soil, *Pub. Health Rep.* **51**: 1496-1505 (Oct. 30) 1936. Smith, M. I., and Westfall, B. B.: Further Field Studies on the Selenium Problem in Relation to Public Health, *ibid.* **52**: 1375-1384 (Oct. 1) 1937.

183. Sterner, J. H., and Lidfeldt, Viola: The Selenium Content of "Normal" Urine, *J. Pharmacol. & Exper. Therap.* **73**: 205-211 (Oct.) 1941. Smith, Franke and Westfall.¹⁸² Smith and Westfall.¹⁸²

184. Several reviews of the selenium problem have appeared recently; (Moxon.¹⁷⁴ Trelease.¹⁷⁰ Smith, M. I.: Chronic Endemic Selenium Poisoning, *J. A. M. A.* **116**: 562-567 [Feb. 15] 1941); in addition, the danger of selenium as an industrial hazard has been noted (Dudley, H. C.: Selenium as a Potential Industrial Hazard, *Pub. Health Rep.* **53**: 281-292 [Feb. 25] 1938).

185. Bertrand, G., and Aquilhon, H.: Sur la présence normale du bore chez les animaux, *Compt. rend. Acad. d. sc.* **155**: 248-251, 1912. Yue, Pao Sen: The Biological Distribution of Boron, dissertation, Johns Hopkins University, May 1937.

186. Hove, E.; Elvehjem, C. A., and Hart, E. B.: Boron in Animal Nutrition, *Am. J. Physiol.* **127**: 689-701 (Nov.) 1939. Wright and Papisch.⁹ Blumberg and Rask.⁹ Drea: Spectrum Analysis for Trace Elements in the Ashes of Human, Goat and Cow Milk.⁹

187. Drea, W. F.: Spectrum Analysis of Hen Eggs and Chick Tissues, *J. Nutrition* **10**: 351-355 (Oct.) 1935. Hove, Elvehjem and Hart.¹⁸⁶

Numerous investigators have observed the rapid urinary excretion of the element.¹⁸⁸ Two recent studies¹⁸⁹ have shown that rats can thrive on diets extremely low in boron (less than 0.8 microgram per rat daily).

ALUMINUM

The use of aluminum in cooking utensils and in baking powders has centered more attention on its possible toxicity than on its role in normal metabolism. The evidence indicates that ingested aluminum is absorbed in but small amounts¹⁹⁰ and that the amounts occurring in the usual human dietary (about 12 to 13 mg. daily¹⁹¹) are not harmful.¹⁹² This element is widely distributed in nature and has been found to occur in very small amounts in plant and animal tissues and in milk.¹⁹³ It is not definitely known at present whether or not aluminum is a dietary essential. Rats maintained for six weeks on a diet containing as little as 1 microgram of aluminum daily appeared normal;¹⁹³ nevertheless, when the aluminum intake was increased there was definite absorption and storage. On the basis of balance studies with young children, Scoular¹⁹⁴ suggests that this element is not essential.

188. Kent, N. L., and McCance, R. A.: The Absorption and Excretion of "Minor" Elements by Man: 1. Silver, Gold, Lithium, Boron and Vanadium, *Biochem. J.* **35**: 837-844 (July) 1941. Hove, Elvehjem and Hart.¹⁹⁴

189. Orent-Keiles, E.: The Role of Boron in the Diet of the Rat, *Proc. Soc. Exper. Biol. & Med.* **44**: 199-202 (May) 1940. Hove, Elvehjem and Hart.¹⁹⁴

190. Among the numerous papers establishing this fact may be mentioned:

McCollum, E. V.; Rask, O. S., and Becker, J. E.: A Study of the Possible Role of Aluminum Compounds in Animal and Plant Physiology, *J. Biol. Chem.* **77**: 753-768, 1928.

Myers, V. C., and Mull, J. W.: The Influence of the Administration of Aluminum on the Aluminum Content of the Tissues and on the Growth and Reproduction of Rats, *ibid.* **78**: 605-613, 1928.

Mackenzie, K.: Excretion and Absorption of Aluminum in the Pig, *Biochem. J.* **24**: 1433-1441, 1930; Excretion and Absorption of Aluminum in the Rat, *ibid.* **25**: 287-291, 1931.

Wührer, J.: Zur Frage der Resorption von Aluminium im Organismus, mit Berücksichtigung des normalen Aluminiumgehalts tierischer Gewebe, *Biochem. Ztschr.* **265**: 169-180, 1933.

Scoular.¹⁹⁴

191. Burn, J. H.: Aluminum and Foods, *Res. Rep. Ext. Ser.* 162 Brit. Non-Ferrous Metals Res. Assn., April 1932, p. 1-29. Beal, G. D.; Unangst, R. B.; Wigman, H. B., and Cox, G. J.: Aluminum Content of Foodstuffs Cooked in Aluminum and in Glass, *Indust. & Engin. Chem.* **24**: 405-407 (April) 1932.

192. Monier-Williams, G. W.: Aluminum in Food, *Reports on Public Health and Medical Subjects* 78, London, Ministry of Health, 1935. Burn.¹⁹¹

193. Hove, E.; Elvehjem, C. A., and Hart, E. B.: Aluminum in the Nutrition of the Rat, *Am. J. Physiol.* **123**: 640-643 (Sept.) 1938.

194. Scoular, Florence I.: A Quantitative Study by Means of Spectrographic Analysis of Aluminum in Nutrition, *J. Nutrition* **17**: 393-405 (April) 1939.

CONCLUSION

Six trace elements, namely iron, copper, iodine, manganese, cobalt and zinc, have been demonstrated to be essential to animal life. Our knowledge of the human requirement for manganese, cobalt and zinc is so meager that the possibility of deficiency of any one of them occurring cannot be dismissed, although, because of their broad distribution in nature and probably small requirement, the likelihood of any acute or widespread deficiency appears remote. The essential trace elements and the other trace elements which occur in living matter but whose importance is unknown stand as a challenge to nutritionists and physiologists. The indispensable "traces," just as the vitamins, appear to be keys to fundamental physiologic processes the mechanisms of which are either only partially understood or in most cases completely unknown.

CHAPTER X

THE FAT SOLUBLE VITAMINS

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An attempt has been made in the present review to outline a few known facts about each fat soluble vitamin and to mention the most recent advances of general interest that have occurred since publication of the symposium on vitamins sponsored by the American Medical Association in 1939. No attempt has been made to delve into many of the details in this field; rather, data have been presented which it is hoped will be of value in orienting conceptions in a rapidly changing subject.

VITAMIN A

CHEMISTRY AND PHYSIOLOGY

The chemistry and physiology of vitamin A and substances having vitamin A activity have been considered in some detail in previous reviews in *THE JOURNAL*.¹

Evidence reveals that there exists, in addition to vitamin A, another compound which has been designated as vitamin A₂. In chemical structure vitamin A₁ is related closely to vitamin A₂; biologically the activity is the same. It appears that vitamin A predominates in the tissues of salt water fish and that vitamin A₂ predominates in the tissues of fresh water fish. The absence of vitamin A₂ in the liver of mammals and other land animals probably can be explained by the absence of vitamin A₂ in their food.²

Vitamin A is a fat soluble compound. Apparently, its absorption is facilitated greatly by the simultaneous absorption of a certain amount of fat. Most investigators agree that the presence of bile is not necessary for proper absorption of vitamin A; however, it still

1. Palmer, L. S.: The Chemistry of Vitamin A and Substances Having a Vitamin A Effect, in *The Vitamins*, Chicago, American Medical Association, 1939, pp. 15-25. Bessey, O. A., and Wolbach, S. B.: Vitamin A: Physiology and Pathology, in *The Vitamins*, pp. 27-54.

2. Gillam, A. E.: The Vitamin A₁ and A₂ Contents of Mammalian and Other Animal Livers, *Biochem. J.* **32**: 1496-1500 (Sept.) 1938. Lovern, J. A., and Morton, R. A.: The Distribution of Vitamins A and A₂: III, *ibid.* **33**: 330-337, 1939. Gray, E. L., and Cawley, J. D.: The Influence of Structure on the Elimination Maximum: The Structure of Vitamin A₂, *J. Biol. Chem.* **134**: 397-401 (June) 1940.

is good therapeutic practice to administer bile salts with concentrates of vitamin A in the treatment of patients who have obstruction of the biliary tract. Esters of vitamin A apparently behave in the intestinal tract in a manner similar to the esters of other fatty acids. Apparently they are hydrolyzed by the enzymes present, and during the height of absorption the vitamin exists in the intestinal wall chiefly as an alcohol.³

The precursors of vitamin A are all the carotenoid pigments commonly called carotene. Since most of vitamin A comes in the form of carotene, some knowledge of its metabolism is important.

Carotene is absorbed less readily than vitamin A and is subject to several more hazards than vitamin A. Carotene apparently requires for its absorption the presence of bile in the intestinal tract. In those conditions in which bile is excluded completely or partially from the intestinal tract or whenever there is a deficiency of bile salts, bile must be given as a supplement in order to assure proper absorption. It also has been demonstrated⁴ that liquid petrolatum can seriously inhibit absorption of carotene. For this reason, liquid petrolatum should not be given immediately after meals.

Storage.—After absorption, the greater portion of carotene is held in the liver, where it gradually disappears in the Kupffer cells as the concentration of vitamin A in the liver increases. In the case of human beings the content of vitamin A, as in all animals, is much lower in the liver at birth, irrespective of the diet of the mother, than in the liver of a normal adult. The liver probably stores about 95 per cent of the reserve of vitamin A in the body and the amount stored is, as a rule, less during childhood and gradually increases with age.⁵ The exact mechanism by which vitamin A is

3. Gray, E. LeB.; Morgareidge, Kenneth, and Cawley, J. D.: Intestinal Absorption of Vitamin A in the Normal Rat, *J. Nutrition* **20**: 67-74 (July) 1940.

4. Curtis, A. C., and Kline, E. M.: Influence of Liquid Petrolatum on Blood Content of Carotene in Human Beings, *Arch. Int. Med.* **63**: 54-63 (Jan.) 1939. Andersen, O.: Effect of Administration of Liquid Paraffin on the Absorption of Vitamin A in Human Subjects, *Hospitaltid.* (supp.) **81**: 29-41, 1938; abstr., *Nutrition Abstr. & Rev.* **8**: 750 (Jan.) 1939.

5. With, T. K.: Undersøgelser over Carotinets Omdannelse til A-Vitamin i Rottens Lever specielt med Henblik paa Processens Hastighed, *Nord. med. tidskr.* **3**: 2901-2903 (Sept.) 1939. Moore, Thomas: Vitamin A and Carotene: XIII. The Vitamin A Reserve of the Adult Human Being in Health and Disease, *Biochem. J.* **31**: 155-164, 1937. Ralli, Elaine P.; Papper, Emanuel; Paley, Karl, and

(Footnote continued on next page)

called forth from its reserve store is not known, but from several sources it appears that the distribution of vitamin A in the circulating blood and tissues is controlled in part by the nervous system.⁶

Excretion.—Neither carotene nor vitamin A is excreted by the kidneys unless an excessive dose of either of these substances has been administered. Carotene is readily excreted in the feces but vitamin A is excreted much less readily. Apparently, unutilized excesses of carotene and vitamin A find other channels of excretion or are destroyed in the intestine or elsewhere.⁷

Human milk contains both carotene and vitamin A. The colostrum of the human breast has from two to three times the biologic activity of vitamin A of early milk, and early human milk has from five to ten times the biologic vitamin A activity of cow's milk. Apparently the biologic activity of vitamin A of early human milk is not increased by supplementary administration of cod liver oil to the mother.

It formerly was believed that vitamin A produced a profound effect on the nervous system.⁸ However, Wolbach and Bessey⁹ have now shown that in vitamin A deficiency in rats, skeletal growth is retarded earlier than that of the soft tissues in general, including that of the central nervous system, and that at least in the white rat the nervous manifestations are due to pressure effects caused by relative overgrowth of the central nervous system.

Bauman, Eli: Vitamin A and Carotene Content of Human Liver in Normal and in Diseased Subjects: An Analysis of One Hundred and Sixteen Human Livers, *Arch. Int. Med.* **68**:102-111 (July) 1941. Cox, A. J., Jr.: Site of Vitamin A Storage in the Liver, *Proc. Soc. Exper. Biol. & Med.* **47**:333-335 (June) 1941. Horton, Priscilla B.; Murrill, W. A., and Curtis, A. C.: Vitamin A and Carotene: I. The Determination of Vitamin A in the Blood and Liver as an Index of Vitamin A Nutrition of the Rat, *J. Clin. Investigation* **20**:387-393 (July) 1941.

6. Chevallier, André: Les facteurs de variation de la réserve hépatique en vitamine A (en particulier l'influence du système nerveux), *Nutrition* **7**:143-146, 1937. Troitzki, G. V.: Influence of the Nerves on the Vitamin A Content of Blood, *Bull. biol. Med. exp. U. R. S. S.* **5**:360-362, 1938; abstr., *Nutrition Abstr. & Rev.* **8**:601 (Jan.) 1939. Young, Genevieve, and Wald, George: The Mobilization of Vitamin A by the Sympathicoadrenal System, *Am. J. Physiol.* **131**:210-215 (Nov.) 1940.

7. Lawrie, N. R.; Moore, T., and Rajagopal, K. R.: Excretion of Vitamin A in Urine, *Biochem. J.* **35**:825-836, 1941. Le Page, G. A. and Pett, L. B.: Absorption Experiments with Vitamin A, *J. Biol. Chem.* **141**:747-761 (Dec.) 1941.

8. Mellanby, Edward: The Experimental Production of Deafness in Young Animals by Diet, *J. Physiol.* **94**:380-398 (Dec. 14) 1938. Irving, J. T., and Richards, M. B.: Early Lesions of Vitamin A Deficiency, *ibid.* **94**:307-321 (Dec. 14) 1938.

9. Wolbach, S. B., and Bessey, O. A.: Vitamin A Deficiency and the Central Nervous System, abstr., *Am. J. Path.* **17**:586 (July) 1941.

SOURCES, HUMAN REQUIREMENTS AND TOXICITY

Vitamin A is rather widespread in nature in the form of its precursors, the yellow and red carotenoid pigments (provitamins). These pigments are found in the plant world, being distributed from bacteria to garden fruits and vegetables. Pigments, of course, are found chiefly in association with chlorophyll and in the green leaves of plants; this is not invariably true, however, since carrots and sweet potatoes, which are yellow, also are rich in these substances. A few of the more important and rich sources of vitamin A and carotene are green leaf vegetables, green snap beans, spinach, carrots, peas, asparagus, yellow vegetables, eggs, whole milk and whole milk products and apricots.

Vitamin A is fairly stable to heat but is destroyed by oxidation. Foods that are heated for long periods may reveal a rather large loss of potency in vitamin A. Since activity of the vitamin is not affected by boiling, foods cooked in this manner retain their potency. Canned foods and foods stored in the frozen state maintain their maximal value of vitamin A; dried and dehydrated foods, however, show considerable loss.

Human Requirements.—Vitamin A is essential for normal metabolism. Although the exact minimal requirement of vitamin A for man is still unknown, considerable work has been carried out in an effort to settle this point.¹⁰ Since the recommended daily allowances for definite nutrients as defined by the Food and Nutrition Board of the National Research Council and later adopted by the Council on Foods and Nutrition of the American Medical Association represent the thoughts of the leaders in these particular fields, it would seem well that these should be accepted without considering other work in this field in any detail.

10. Booher, Lela E.; Callison, Elizabeth C., and Hewston, Elizabeth M.: An Experimental Determination of the Minimum Vitamin A Requirements of Normal Adults, *J. Nutrition* **17**:317-331 (April) 1939. May, C. D.; Blackfan, K. D.; McCreary, J. F., and Allen, F. H., Jr.: Clinical Studies of Vitamin A in Infants and in Children, *Am. J. Dis. Child.* **59**:1167-1184 (June) 1940. Lewis, J. M., and Haig, C.: Vitamin A Requirements in Infancy as Determined by Dark Adaptation, *J. Pediat.* **15**:812-823 (Dec.) 1939; correction, *ibid.* **16**:274 (Feb.) 1940. Booher, Lela E., and Callison, Elizabeth C.: The Minimum Vitamin A Requirements of Normal Adults, the Utilization of Carotene as Affected by Certain Dietary Factors and Variations in Light Exposure, *J. Nutrition* **18**:459-471 (Nov.) 1939, Sandels, Cate, Wilkinson and Graves.¹¹

For the average man and woman of 70 Kg. and 56 Kg. respectively, the daily allowance is 5,000 international units. In the latter half of pregnancy, 6,000 international units is required, and during lactation 8,000 international units. For children aged less than a year, 1,500 units is required; for those aged 1 to 3 years, 2,000; for those from 4 to 6 years, 2,500; for those from 7 to 9 years, 3,500, and for those from 10 to 12 years, 4,500. For children more than 12 but not more than 15 years of age, 5,000 units is required, and for those from 16 to 20 years of age, 6,000 units. Allowances in all these instances may be less if provided by vitamin A and greater if provided chiefly by the provitamin carotene.

Toxicity.—It is extremely difficult to evaluate the few reports concerning the injurious effects on man following ingestion of cod liver oil. Owing to the general favorable clinical experience obtained in the use of cod liver oil and other preparations containing vitamin A, extreme care must be taken to be certain that cod liver oil is harmful before its administration is discontinued. Administration of from 50,000 to 300,000 or more U. S. P. units of vitamin A daily for as long as two to six months or more has not been followed by any harmful effects.¹¹

EFFECT OF DEFICIENCY OF VITAMIN A

In Relation to Infection.—Few investigators doubt that severe deficiency of vitamin A, or any vitamin, will lower resistance to infection, and almost all will agree that administration of vitamin A during the course of any infection will have little beneficial effect on the outcome unless such a deficiency is present. Some workers believe that the frequency and high mortality rate in pneumonia of infants who are deficient in vitamin A result from a disturbance of function of the mucosa of all parts of the lungs. Others believe that administration of vitamin A in large amounts is beneficial in preventing common infections of the respiratory tract. This subject, however, is in general extremely controversial. Enough evidence indicates that there are many other factors of equal or greater influence in infection than vitamin A and that there is no justification for calling vitamin A the "anti-infection vitamin."

11. Straumfjord.²⁰ Lehman and Rapaport.²¹

Ocular Changes.—That night blindness is directly related to poor nutrition has been recognized for some time. Experimentally it is now established that vitamin A is the precursor of visual purple as well as the product of its decomposition. Apparently vitamin A unites in the retina with a protein to form visual purple. This, of course, takes place continuously and depends on a sufficient supply of vitamin A. Exposure of the retina to light leads to a chemical change which is reversible but which is not always efficient, and therefore needed supplies of vitamin A must always be available. Not only does vitamin A play a part in metabolism of visual purple (rhodopsin), but it is also important in the formation of visual violet (iodopsin), which is present in the retinal cones.¹² Not only does deficiency of vitamin A produce night blindness but, experimentally, it has been demonstrated that severe deficiency of vitamin A may result in structural breakdown of the retina itself.¹³ Night blindness, as recognized clinically, perhaps is associated most frequently with cirrhosis of the liver,¹⁴ gastrocolic fistula¹⁵ and forms of severe chronic diarrhea.

It has been thought that night blindness was one of the earliest symptoms of deficiency of vitamin A, but Kruse¹⁶ suggested recently that even earlier changes of deficiency may be detected by biomicroscopic examination. In a study of 143 persons in the low income group it was reported that 45 per cent had gross and 54 per cent had microscopic ocular lesions (xerosis conjunctivae) characteristic of avitaminosis A. It also was suggested that xerosis conjunctivae probably precedes night blindness as an early sign of deficiency of vitamin A. Kruse suggested that this condition is prevalent in the population at large, and he also pointed out that a vascular reaction of the eyes of these patients is distinct from that noted as a result of deficiency of

12. Wald, George, and Steven, David: An Experiment in Human Vitamin A Deficiency, *Proc. Nat. Acad. Sc.* **25**: 344-349 (July) 1939.

13. Johnson, Myra L.: The Effect of Vitamin A Deficiency on the Retina of the Rat, *J. Exper. Zool.* **51**: 67-89 (June) 1939.

14. Patek, A. J., Jr., and Haig, Charles: The Occurrence of Abnormal Dark Adaptation and Its Relation to Vitamin A Metabolism in Patients with Cirrhosis of the Liver, *J. Clin. Investigation* **18**: 609-616 (Sept.) 1939.

15. Butt, H. R.: Unpublished data.

16. Kruse, H. D.: Medical Evaluation of Nutritional Status: IV. The Ocular Manifestations of Avitaminosis A, with Especial Consideration of the Detection of Early Changes by Biomicroscopy, *Pub. Health Rep.* **56**: 1301-1324 (June 27) 1941.

riboflavin. Others¹⁷ have reported that follicular conjunctivitis occurring among children apparently is a result of deficiency of vitamin A. These workers pointed out that the administration of from 25,000 to 38,000 U. S. P. units of vitamin A daily did not result in any more rapid healing than if only 15,000 U. S. P. units had been given. Apparently, in treatment of conditions with vitamin A, a time factor operates which limits the rate of healing of a lesion. Apparently excessive intake of vitamin A does not increase this rate proportionately.

Epithelium.—Dryness and scaliness of the skin are perhaps some of the earliest manifestations of involvement of the skin resulting from deficiency of vitamin A. Within the past few years several investigators have reported cases in which cutaneous lesions were present and which were considered the result of deficiency of vitamin A.¹⁸ One type of lesion is characterized by small pustules which appear around the hair follicles or extensor surfaces of the upper and lower extremities, on the shoulder and on the lower part of the abdomen and buttocks. These pustules vary in diameter up to 5 mm., are hard and deeply pigmented and have a surrounding zone of deep pigmentation. An epithelial plug is in the center of the lesion which, when expressed, leaves a crater. Other writers have described a type of lesion which resembles in many ways the pustule of acne, with the exception that pustulation is uncommon. It is believed¹⁹ that keratosis pilaris, ichthyosis follicularis and other synonyms are descriptive terms for the cutaneous manifestations of deficiency of vitamin A. In treatment of such conditions daily doses of 100,000 to 300,000 international units of vitamin A is given for two or three months before beneficial effects are noted. It is pointed out that response of cutaneous lesions to vitamin A is slow, depending as it does on anatomic repair.

17. Sandels, Margaret R.; Cate, Helen D.; Wilkinson, Kathleen P., and Graves, L. J.: Follicular Conjunctivitis in School Children as an Expression of Vitamin A Deficiency, *Am. J. Dis. Child.* **62**:101-114 (July) 1941.

18. Rao, M. V. R.: Treatment of Phrynoderma by Vitamin A Concentrate, *Indian M. Gaz.* **73**:461-462 (Aug.) 1938. Lehman and Rapaport.¹⁹

19. Lehman, Edward, and Rapaport, H. G.: Cutaneous Manifestations of Vitamin A Deficiency in Children, *J. A. M. A.* **114**:386-393 (Feb. 3) 1940.

Recently²⁰ evidence has been reported which indicates that vernix caseosa is a manifestation of deficiency of vitamin A of newborn infants and that it represents disturbances in cornification analogous to the dermal changes noted in other manifestations of deficiency of vitamin A. This work has not yet been confirmed.

A majority of investigators have failed to find any relation between the presence of calculi in the urinary tract and a diet deficient in vitamin A, in spite of suggestive experimental evidence in this direction.²¹

Liver.—It has been established that the liver plays a major role in the metabolism of vitamin A, but the exact manner in which this is accomplished is not known. It has been known for many years that keratomalacia and night blindness accompany diseases of the liver, and recently these conditions have been reported²² in association with obstructive biliary cirrhosis. Others²³ have demonstrated deficiency of vitamin A in cirrhosis of the liver not associated with jaundice. Many others have demonstrated repeatedly that the vitamin A in the liver and blood of patients who have severe hepatic injury nearly always is decreased considerably.²⁴ It has been suggested that since pathologic conditions of the liver result in incom-

20. Straumfjord, J. V.: Vernix Caseosa: A Manifestation of Vitamin A Deficiency; a Preliminary Report, *West. J. Surg.* **48**: 341-351 (June) 1940.

21. Ezickson, W. J., and Feldman, J. B.: Further Studies of Vitamin A Deficiency in Individuals with Urinary Lithiasis: A Report of Further Clinical Studies and Investigations on Thirty-Six Patients, *Urol. & Cutan. Rev.* **43**: 302-304 (May) 1939.

22. Stone, J. B., and Courtney, R. H.: Xerophthalmia and Keratomalacia Associated with Obstructive Biliary Cirrhosis, *Virginia M. Monthly* **68**: 159-163 (March) 1941.

23. Patek, A. J., Jr., and Haig, Charles: The Occurrence of Abnormal Dark Adaptation and Its Relation to Vitamin A Metabolism in Patients with Cirrhosis of the Liver, *J. Clin. Investigation* **18**: 609-616 (Sept.) 1939.

24. Moore, T.: Vitamin A and Carotene: The Vitamin A Reserve of the Adult Human Being in Health and Disease, *Biochem. J.* **31**: 155-164 (Jan.) 1937. Chevallier, André; Omer, Jean, and Vague, J.: Sur la valeur diagnostique et pronostique du taux de l'hémovitaminine au cours des hépatites, *Bull. et mém. Soc. méd. d. hôp. de Paris* **2**: 928-932 (June 9) 1939. Lasch, Fritz: Ueber den Vitamin A-Spiegel im Blute bei Leberkrankheiten, *Klin. Wchnschr.* **17**: 1107-1108 (Aug. 6) 1938. Jensen, H. B., and With, T. K.: Vitamin A and the Carotenoids in the Liver of Mammals, Birds, Reptiles and Man with Particular Regard to the Intensity of the Ultraviolet Absorption and the Carr-Price Reaction of Vitamin A, *Biochem. J.* **33**: 1771-1786 (Nov.) 1939. Woo, Theresa T., and Chu, F. T.: The Vitamin A Content of the Livers of Chinese Infants, Children and Adults, *Chinese J. Physiol.* **15**: 83-100 (Jan.) 1940. Wohl, M. G., and Feldman, J. B.: Vitamin A Deficiency in Diseases of the Liver: Its Detection by Dark-Adaptation Method, *J. Lab. & Clin. Med.* **25**: 485-494 (Feb.) 1940. Woodruff, M. F. A., and Wright, R. D.: The Diagnosis, Incidence and Treatment of Avitaminosis A and D in Obstructive Jaundice, *Australian & New Zealand J. Surg.* **10**: 135-145 (Oct.) 1940.

plete transformation of carotene into vitamin A, fish liver oil should be given in preference to carotene in the treatment of hepatic disease.²⁵

It is obvious that deficiency of vitamin A also may result from poor absorption of the vitamins, such as may occur in diarrhea,²⁶ celiac disease²⁷ and various diseases of the liver in which the flow of bile is disrupted.²⁸

METHODS FOR MEASURING DEFICIENCY OF VITAMIN A

Dark Adaptation.—The fact that night blindness is an early symptom of deficiency of vitamin A led to the development of visual adaptation in dim light as a method for the diagnosis of deficiency of vitamin A. Whether deficiency of vitamin A can be measured by testing adaptation to dark continues to be a most controversial subject. Some contend that this method is satisfactory for measuring deficiency of vitamin A.²⁹ Others³⁰ contend that, although some rela-

25. Monceaux, R. H.: Difficulté de transformation du carotène en facteur A au cours de nombreux états pathologiques; conséquences thérapeutiques, *J. de pharm. et chim.* **28**:297-302, 1938; abstr. *Nutrition Abstr. & Rev.* **8**:1062 (April) 1939.

26. Goldberg, H. K., and Schlivek, Kaufman: Necrosis of the Cornea Due to Vitamin A Deficiency: Report of a Case, *Arch. Ophthalm.* **25**:122-127 (Jan.) 1941.

27. May, C. D., and McCreary, J. F.: The Absorption of Vitamin A in Celiac Disease; Interpretation of the Vitamin A Absorption Test, *J. Pediat.* **18**:200-209 (Feb.) 1941. Lindqvist, T.: Studien über das vitamin A beim Menschen, *Acta med. Scandinav. (suppl.)* **97**:1-52, 1938. Breese, B. B., Jr., and McCoord, Augusta B.: Vitamin A Absorption in Celiac Disease, *J. Pediat.* **15**:183-196 (Aug.) 1939.

28. Breese, B. B., and McCoord, Augusta B.: Vitamin A Absorption in Catarrhal Jaundice, *J. Pediat.* **16**:139-145 (Feb.) 1940. Salah, M.: Vitamin A Deficiency in Jaundice, *J. Egyptian M. A.* **23**:153-161 (March) 1940.

29. Hecht, Selig, and Mandelbaum, Joseph: The Relation Between Vitamin A and Dark Adaptation, *J. A. M. A.* **112**:1910-1916 (May 13) 1939. Caussade, L.; Neimann, N.; Thomas, C., and Davidsohn: Recherches sur les tests oculaires d'hypovitaminose A chez les enfants d'âge scolaire, *Rev. franç. de pédiat.* **14**:209-223, 1938; abstr. *J. A. M. A.* **112**:676 (Feb. 18) 1939. Thomson, A. M.; Griffith, H. D.; Mutch, J. R., and Lubbock, D. M., with the assistance of Owen, E. C., and Logaras, J.: A Study of Diet in Relation to Health; Dark Adaptation as an Index of Adequate Vitamin A Intake: II. A New Photometer for Measuring Rate of Dark Adaptation, *Brit. J. Ophthalm.* **23**:461-478 (July) 1939. Pett, L. B.: A Rapid Visual Test for Vitamin A Deficiency, *Nature, London* **143**:23 (Jan. 7 1939). Steele, E. J. P.: Effect of Vitamin A Therapy Estimated by a Rapid Optical Test, *Lancet* **2**:205-206 (Aug. 17) 1940. Sheftel, A. G.: Dark Adaptation and Vitamin A Deficiency: A New Technic, *Am. J. Clin. Path.* **10**:168-175 (Feb.) 1940. Pett, L. B.: Vitamin A Deficiency: Its Prevalence and Importance as Shown by a New Test, *J. Lab. & Clin. Med.* **25**:149-160 (Nov.) 1939. Blanchard, E. L., and Harper, H. A.: Measurement of Vitamin A Status of Young Adults by the Dark Adaptation Technic, *Arch. Int. Med.* **66**:661-669 (Sept.) 1940. McDonald, Robb, and Adler, F. H.: Effect of Anoxemia on the Dark Adaptation of the Normal and of the Vitamin A Deficient Subject, *Arch. Ophthalm.* **22**:980-987 (Dec.) 1939. Eckardt, R. E., and Johnson, L. V.: A Comparison of Two Methods of

tion exists between readings of the biophotometer and of nutrition of vitamin A, yet the relation is not close enough to warrant use of the test as a means of diagnosis of subclinical deficiency of vitamin A. It has been pointed out that the method is time consuming, and for this reason alone its routine clinical use practically is ruled out. Certainly, minor fluctuations in dark adaptation in terms of deficiency of vitamin A should receive little emphasis unless the physical methods are used to test the reliability of the differences. It is true that a majority of workers believe that the study of dark adaptation can be used as a test for deficiency of vitamin A, but until differences in technic and in interpretation of results have been resolved it is impossible to be certain how far recorded observations represent physiologic facts. In fact, by placing human beings on a diet deficient in vitamin A over long periods, some investigators³¹ have been unable to produce clinical night blindness or even changes in dark adaptation. It may be, as stated by Josephs,³² that all this discrepancy may be the result of lack of knowledge of methods for determining sufficient storage of vitamin A.

No definite correlation between biophotometer readings and the content of vitamin A in the blood has

Measuring Dark Adaptation, *J. Pediat.* **18**:195-199 (Feb.) 1941. Jeaus, P. C.; Blanchard, Evelyn L., and Satterthwaite, F. E.: Dark Adaptation and Vitamin A: Further Studies with the Biophotometer, *ibid.* **18**: 170-194 (Feb.) 1941.

30. Snelling, C. E.: The Biophotometer as a Test for Vitamin A Deficiency, *J. Pediat.* **13**: 506-509 (Oct.) 1938. Steininger, Grace, and Roberts, Lydia J.: Biophotometer Test as Index of Nutritional Status for Vitamin A, *Arch. Int. Med.* **64**: 1170-1186 (Dec.) 1939. Harris, L. J., and Abbasy, M. A.: The Dark-Adaptation Test: Its Reliability as a Test for Vitamin A Deficiency, *Lancet* **2**: 1299-1305 (Dec. 23); 1355-1359 (Dec. 30) 1939. Isaacs, B. L.; Jung, F. T., and Ivy, A. C.: Clinical Studies of Vitamin A Deficiency: Biophotometer and Adaptometer (Hecht) Studies on Normal Adults and on Persons in Whom an Attempt was Made to Produce Vitamin A Deficiency, *Arch. Ophth.* **24**: 698-721 (Oct.) 1940; correction, *ibid.* **25**: 158 (Jan.) 1941. Thomson, A. M.; Griffith, H. D.; Mutch, J. R.; Lubbock, D. M.; Owen, E. C., and Logaras, G.: A Study of Diet in Relation to Health: Dark Adaptation as an Index of Adequate Vitamin A Intake: III. The Relation of Diet to Rate and Extent of Dark Adaptation, *Brit. J. Ophth.* **23**: 697-723 (Nov.) 1939. Dann, W. J., and Yarbrough, M. E.: Dark Adaptometer Readings of Subjects on a Diet Deficient in Vitamin A, *Arch. Ophth.* **25**: 833-838 (May) 1941. Stewart, C. P.: Nutritional Factors in Dark Adaptation, *Edinburgh M. J.* **48**: 217-237 (April) 1941.

31. Jung, F. T., and Isaacs, B. L.: Measurement of Vitamin A Deficiency in Man, *Proc. Inst. Med. Chicago* **12**: 317-318 (March 15) 1939. Steffens, L. F.; Bair, H. L., and Sheard, Charles: Photometric Measurements on Visual Adaptation in Normal Adults on Diets Deficient in Vitamin A, *Proc. Staff Meet., Mayo Clin.* **14**: 698-704 (Nov. 1) 1939.

32. Josephs, H. W.: Studies in Vitamin A: Relation of Vitamin A and Carotene to Serum Lipids, *Bull. Johns Hopkins Hosp.* **65**: 112-124 (July) 1939.

been observed.³³ Although it has been demonstrated that the amount of vitamin A in the blood is dependent on the amount in the diet, yet evidence as to whether determination of vitamin A in the blood is of value in judging the nutritional status is still contradictory. Recently evidence has been presented which suggests that the concentration of vitamin A in the blood plasma is a considerably more sensitive indicator of deficiency of vitamin A than the dark adaptation.³⁴

The same contradictory evidence is presented for measuring vitamin A by examination of scrapings from the eye and vagina. From all these studies it would be judged that the methods for measuring deficiency of vitamin A of man still are somewhat unreliable and demand further study. Among some physicists and chemists there still is doubt whether the small quantities of vitamin A present in the blood stream of man can be measured with the chemical methods available. There are others who feel that no satisfactory chemical methods can be developed until the storage capacity of the body for vitamin A can be estimated in some degree.

VITAMIN D

Since the time (1922) of McCollum's demonstration that vitamin D is distinct from vitamin A, this vitamin (D) has received perhaps the greatest universal attention of any. Here, in the early history of nutritional investigation, was found a substance which was of value in the prevention and cure of a disease.

CHEMICAL ASPECTS

Some ten forms of vitamin D are known, but only two of them are of practical importance. One is ergosterol, which on exposure to ultraviolet light becomes viosterol (a name adopted by the Council on

33. Baum, W. S., and McCoord, Augusta B.: The Relationship Between Biophotometer Tests and the Vitamin A Content of the Blood of Children, *J. Pediat.* **16**: 409-418 (April) 1940. Steininger, Grace; Roberts, Lydia J., and Brenner, Sadie: Vitamin A in the Blood of Normal Adults: The Effect of a Depletion Diet on Blood Values and Biophotometer Readings, *J. A. M. A.* **113**: 2381-2387 (Dec. 30) 1939. Caveness, H. L.; Satterfield, G. H., and Dann, W. J.: Correlation of the Results of the Biophotometer Test with the Vitamin A Content of Human Blood, *Arch. Ophth.* **25**: 827-832 (May) 1941. Josephs, H. W.; Baber, Margaret, and Conn, Howard: Studies in Vitamin A: Relation of Blood Level and Adaptation to Dim Light to Diet, *Bull. Johns Hopkins Hosp.* **68**: 375-387 (May) 1941.

34. Bodansky, Oscar; Lewis, J. M., and Haig, Charles: The Comparative Value of the Blood Plasma Vitamin A Concentration and the Dark Adaptation as a Criterion of Vitamin A Deficiency, *Science* **64**: 370-371 (Oct. 17) 1941.

Pharmacy and Chemistry of the American Medical Association). The other form of vitamin D of practical use is activated 7-dehydrocholesterol. This substance is present in animal fats, and its active form is produced in the skin, feathers or furs of animals exposed to sunlight or other sources of ultraviolet waves.³⁵ Successful synthesis of compounds related to the antirachitic vitamins has been reported, and it is hoped that a suitable product soon will be available.³⁶

PHYSIOLOGIC ASPECTS

The active vitamin D formed in the skin is absorbed by the blood. When the vitamin is ingested it is readily absorbed from the intestinal tract if adequate amounts of bile salts are present. Results of recent investigations indicate that the salts of desoxycholic acid may be particularly concerned with the absorption of the liposoluble vitamins.

The chief storehouse of vitamin D in the human being is the liver, but significant amounts are stored also in the skin, brain, lungs, spleen and bones.³⁷ Moreover, although the liver is the chief storehouse of the vitamin, normal hepatic function is necessary to promote the antirachitic action of vitamin D.

The body apparently has great powers for the conservation of vitamin D. Studies on the excretion of vitamin D are lacking, but it is known that small doses of vitamin D will exert an influence which endures for several weeks and that large doses of it are carefully preserved for a long time.

Concentration of vitamin D in the blood has been studied inadequately, and in view of methods presently available such studies are impracticable for even a well equipped laboratory to carry out.³⁸

35. Bills, C. E.: *The Chemistry of Vitamin D*, in *The Vitamins*, Chicago, American Medical Association, 1939, pp. 443-458.

36. Milas, N. A., and Alderson, W. L., Jr.: *Studies in the Synthesis of the Antirachitic Vitamins: I. The Synthesis of 3-[2'Methylene-cyclohexylidene-1']-Propene-1*, *J. Am. Chem. Soc.* **61**: 2534-2537 (Sept.) 1939. Aldersley, J. B.; Burkhardt, G. N.; Gillam, A. E., and Hindley, N. C.: *The Synthesis of Compounds Related to the Antirachitic Vitamins: Part II*, *J. Chem. Soc. London*, part 1 (Jan.) 1940, pp. 10-16.

37. Vollmer, Hermann: *Distribution of Vitamin D in Body After Administration of Massive Doses*, *Am. J. Dis. Child.* **57**: 343-348 (Feb.) 1939. Vollmer, Hermann: *Distribution of Vitamin D in the Brain After Repeated Administration of Massive Doses; Histologic Investigation of D-Hypervitaminosis*, *Arch. Pediat.* **58**: 9-20 (Jan.) 1941.

38. Warkany, Josef, and Mabon, Helen E.: *Estimation of Vitamin D in Blood Serum: II. Level of Vitamin D in Human Blood Serums*, *Am. J. Dis. Child.* **60**: 606-614 (Sept.) 1940.

The exact role of vitamin D in the metabolism of calcium and phosphorus still is not fully established. The action of vitamin D on calcium and phosphorus metabolism, however, seems to be concerned chiefly with absorption of the elements from the intestinal tract. In carefully conducted studies,³⁹ it has been reported that one of the first signs of deficiency of vitamin D is the decrease in the amount of calcium in the urine, followed by an increase of calcium in the stool which progresses with the deficiency until a negative calcium balance exists. The changes in the metabolism of phosphorus differ only in the fact that the urinary excretion of phosphorus is increased. These changes can be reversed with very small doses of vitamin D. Results of other studies tend to confirm these observations.⁴⁰

There exists in the body an enzyme, phosphatase, which is related intimately to phosphorus metabolism. Its exact function in the serum is not known, but in active rickets the value for phosphatase in the serum is high. The administration of vitamin D under these circumstances decreases the concentration toward normal but more slowly than it increases the concentration of calcium and phosphorus.

DISTRIBUTION, HUMAN REQUIREMENT AND TOXICITY

Vitamin D is an essential vitamin but is contained in only a few of the foods in the average American diet. Small amounts are present in eggs, herring, sardines, tuna and salmon, either fresh or canned.⁴¹ Contrary to a popular misconception, butter contains only a very small amount of vitamin D.

Since the average diet furnishes so little vitamin D, it must be assumed either that the requirement of vitamin D for man is extremely low or that his needs

39. Liu, S. H.: The Role of Vitamin D in the Calcium Metabolism in Osteomalacia, *Chinese M. J.* **57**: 101-118 (Feb.) 1940. Liu, S. H.; Chu, H. I.; Su, C. C.; Yu, T. F., and Cheng, T. Y.: Calcium and Phosphorus Metabolism in Osteomalacia: IX. Metabolic Behavior of Infants Fed on Breast Milk from Mothers Showing Various States of Vitamin D Nutrition, *J. Clin. Investigation* **19**: 327-347 (March) 1940. Chu, H. I.; Liu, S. H.; Yu, T. F.; Hsu, H. C.; Cheng, T. Y., and Chao, H. C.: Calcium and Phosphorus Metabolism and Osteomalacia: X. Further Studies on Vitamin D Action: Early Signs of Depletion and Effect of Minimal Doses, *ibid.* **19**: 349-363 (March) 1940.

40. Albright, Fuller; Sulkowitch, H. W., and Bloomberg, Esther: A Comparison of the Effects of Vitamin D, Dihydrotachysterol (A. T. 10), and Parathyroid Extract on the Disordered Metabolism of Rickets, *J. Clin. Investigation* **18**: 165-169 (Jan.) 1939.

41. Lindsay, Jessie, and Mottram, V. H.: Vitamin D in Diet: Palatable Methods of Supply, *Brit. M. J.* **1**: 14-15 (Jan. 7) 1939.

usually are provided by exposure to sunshine. The requirement of vitamin D during adult life, therefore, remains to be determined. Vitamin D undoubtedly is necessary for older children and adult persons, and when not available from sunshine it should be provided, probably up to the minimal amounts recommended for infants. During pregnancy and lactation and for children under a year of age, 400 to 800 international units of vitamin D is the daily requirement recommended by the Food and Nutrition Board of the National Research Council. In administering antirachitic agents the physician should think in terms of units of vitamin D, since this is the only way in which the doses of the various substances containing vitamin D, which differ greatly in volume, can be reduced to a common denominator.

When doses of vitamin D many times the therapeutic dose are administered to animals, certain pathologic changes are noted. In the human being, however, no serious toxic effects have been reported in cases in which doses of as much as 1,000,000 units have been administered to rachitic children.⁴² Some adult persons treated with large doses of vitamin D have complained of nausea, headache, diarrhea, anorexia, urinary frequency and lassitude. If renal insufficiency exists, it might be feared that some degree of toxicity would result from overdosage with vitamin D.⁴³

CLINICAL USE

Little can be added to the comprehensive article by Jeans and Stearns⁴⁴ on the clinical usefulness and available sources of vitamin D which appeared in the symposium on vitamins sponsored by the American Medical Association in 1939. This and several other comprehensive reviews⁴⁵ deal most adequately with this problem, and there seems little need of much repetition. Other sections to be presented in this review also will deal with the clinical use and value of vitamin D.

42. Gunnarson, Siv: Treatment of Rickets with a Single Massive Dose of Vitamin D₂, *Acta paediat.* **25**: 69-81, 1939.

43. Oppel, Lincoln: Effect of Renal Damage on the Toxicity of Hypervitaminosis D in Rats, *Arch. Path.* **31**: 569-577 (May) 1941. Tumulty, P. A., and Howard, J. E.: Irradiated Ergosterol Poisoning: Report of Two Cases, *J. A. M. A.* **109**: 233-236 (May 16) 1942.

44. Jeans, P. C., and Stearns, Genevieve: The Human Requirement of Vitamin D, in *The Vitamins*, Chicago, American Medical Association, 1939, pp. 483-512.

45. Kramer, Benjamin: Vitamin D Therapy, *J. Mt. Sinai Hosp.* **8**: 188-209 (Sept.-Oct.) 1941. Park.⁴⁶

The suggestion made by Park,⁴⁶ however, in the treatment of rickets will again bear emphasis. For preventive measures the importance of commencing administration of the vitamin early and reaching the full dose "certainly by the end of the second month" of the infant's life cannot be repeated too often. In the active treatment of rickets, milk containing vitamin D does not exhibit sufficient activity to end the disease abruptly, and doses of vitamin D sufficient to furnish 1,000 U. S. P. units daily, or even 10,000 to 20,000 units to premature infants, may be required.

The treatment of active rickets with large, single parenteral doses of vitamin D has received considerable attention during the past two years.⁴⁷ Administration of 500,000 to 1,000,000 U. S. P. units of vitamin D to children who had rickets (including premature infants) has been followed by rapid healing without clinical evidence of toxicity.

Many other diseases unrelated to rickets have been reported as benefited by the administration of vitamin D. Pemphigus,⁴⁸ chronic ulcers of the extremities⁴⁹ and psoriasis⁵⁰ are only a few conditions reported as benefited thereby. Most of the results reported have not been confirmed.

VITAMIN E

When it is compared to the other vitamins, vitamin E assumes a rather unsatisfactory position, since it has never been demonstrated that a deficiency of this substance occurs in man. As early as 1922 the necessity of this factor (then called "factor X") was recognized in animals, and in spite of a host of brilliant chemical and physiologic discoveries clinical attempts at application of this knowledge have resulted only in controversy.

46. Park, E. A.: The Therapy of Rickets, *J. A. M. A.* **115**: 370-379 (Aug. 3) 1940.

47. Ström, Justus: The Treatment of Spasmophilia with a Single Massive Dose of Vitamin D₂, *Acta paediat.* **25**: 251-265, 1939. Vollmer, Hermann: Treatment of Rickets and Tetany by Parenteral Administration of One Massive Dose of Vitamin D, *J. Pediat.* **16**: 419-432 (April) 1940. Zelson, Carl: Prevention of Rickets in Premature Infants with Parenteral Administration of Single Massive Doses of Vitamin D, *ibid.* **17**: 73-78 (July) 1940. Gunnarson.⁴⁸

48. King, Howard, and Hamilton, C. M.: Pemphigus Controlled by Vitamin D, *Arch. Dermat. & Syph.* **39**: 515-517 (March) 1939.

49. Brandaleone, Harold: The Effect of the Direct Application of Cod Liver Oil on the Healing of Ulcers of the Feet in Patients with Diabetes Mellitus, *Ann. Surg.* **108**: 141-152 (July) 1938.

50. Krafka, Joseph: Vitamin D Therapy in Psoriasis, *J. M. A. Georgia* **30**: 398-400 (Sept.) 1941.

CHEMICAL AND PHYSIOLOGIC PROPERTIES

Recent advances in the knowledge of vitamin E have been confined in a large measure to the field of chemistry and experimental animal physiology. Details of these advances may be found in journals or books devoted to this subject.⁵¹ Suffice it herein to say that there are now more than one hundred and thirty compounds which exhibit vitamin E activity. The most active of these compounds are the tocopherols. The tocopherols are readily soluble in lipid solvents, resist high temperatures and lose their activity in the presence of mild oxidizing agents. It has been postulated that in the living organism vitamin E might act as a respiratory enzyme.

In animals a lack of vitamin E manifests itself chiefly by changes which it causes in the reproductive mechanism and in the muscular and nervous systems. In the female rat conception is followed by "resorptive sterility," and in the male rat degeneration of the germinal epithelium and spermatozoa develops to the point of complete loss of reproductive power. Absence of vitamin E in certain animals (rabbits and guinea pigs) is followed by muscular dystrophy and a characteristic paralysis of the hindquarters. In other animals (chicks) encephalomalacia and exudative diathesis may develop.

51. Mattill, H. A.: Vitamin E, in *The Vitamins*, Chicago, American Medical Association, 1939, pp. 575-596. Smith, L. I.: *The Chemistry of Vitamin E*, Chem. Rev. **27**: 287-329 (Oct.) 1940. Vitamin E, New York, Chemical Publishing Co., Inc., 1940. Evans, H. M.; Emerson, O. H.; Emerson, G. A.; Smith, L. I.; Ungnade, H. E.; Frichard, W. W.; Austin, F. L.; Hoehn, H. H.; Opie, J. W., and Wawzonek, S.: *The Chemistry of Vitamin E: XIII. Specificity and Relationship Between Chemical Structure and Vitamin E Activity*, J. Organ. Chem. **4**: 376-388 (Sept.) 1939. Ridgway, R. R.; Drummond, J. C., and Wright, Margaret D.: *The Biological Activity of the Oxidation Products of α -Tocopherol*, Biochem. J. **34**: 1569-1573 (Dec.) 1940. Tishler, Max, and Evans, H. M.: *Vitamin E Activities of Some Compounds Related to α -Tocopherol*, J. Biol. Chem. **139**: 241-245 (May) 1941. Pappenheimer, A. M.: *Certain Nutritional Disorders of Laboratory Animals Due to Vitamin E Deficiency*, J. Mt. Sinai Hosp. **7**: 65-76 (July-Aug.) 1940. Pappenheimer, A. M., and Goettsch, Marianne, with the assistance of Karsubova, Claudia: *Effect of Nerve Section on Development of Nutritional Muscular Dystrophy in Young Rats*, Proc. Soc. Exper. Biol. & Med. **43**: 313-316 (Feb.) 1940. Anderson, H. D.; Elvehjem, C. A., and Gonce, J. E., Jr.: *Vitamin E Deficiency in Dogs*, *ibid.* **43**: 750-755 (Dec.) 1939. Friedman, Irving, and Mattill, H. A.: *The Oxygen Consumption of Skeletal Muscle from Animals Deprived of Vitamin E*, Am. J. Physiol. **131**: 595-600 (Jan.) 1941. Mackenzie, C. G.; Mackenzie, J. B., and McCollum, E. V.: *Uncomplicated Vitamin E Deficiency in the Rabbit and Its Relation to the Toxicity of Cod Liver Oil*, J. Nutrition **21**: 225-234 (March) 1941. Dam, Henrik; Glavind, Johannes; Inge, Frange, and Ottesen, J.: *Some Studies on Vitamin E*, Biologiske Meddelelsee, 1941, vol. 16. Mackenzie, C. G., and McCollum, E. V.: *The Cure of Nutritional Muscular Dystrophy in the Rabbit by Alpha-Tocopherol and Its Effect on Creatine Metabolism*, J. Nutrition **19**: 345-362 (April) 1940. Adamstone, F. B.: *Brain Degeneration in Young Chicks Reared on an Iron-Treated Vitamin E-Deficient Ration*, Arch. Path. **31**: 603-612 (May) 1941.

The possible relationship of vitamin E to the glands of internal secretion and to the growth of tumors has stimulated a great amount of experimental work, but results are completely controversial.⁵²

Several methods exist for the chemical and biologic estimation of vitamin E, but they are of little importance to the clinician.

SOURCES, HUMAN REQUIREMENT AND TOXICITY

Wheat germ oil is the richest source of vitamin E, but this vitamin also is found in considerable amounts in cottonseed oil, lettuce oil, rice germ oil and other seed germ oils. The human requirements of vitamin E are completely unknown.

No toxic reactions have been reported in cases in which small doses were administered, and large doses of wheat germ oil have given rise only to minor symptoms. The danger of the production of neoplasms after the continued ingestion of large doses of tocopherols appears to be nonexistent.

CLINICAL USE

If the physician makes only a cursory appraisal of the current literature he may be led to believe that in vitamin E he has a potent weapon for his attack on habitual abortion, sterility, menstrual disturbances and various myoneurogenic diseases. A critical analysis of these numerous reports, however, tends to stem over-enthusiasm.⁵³

The Reproductive System.—A number of papers in which the treatment of habitual abortion with vitamin E is considered have appeared, but when one considers the inherent difficulty of making the diagnosis of habitual abortion, plus the absence of knowledge of the outcome in cases in which treatment is completely lacking, then one is impressed with the almost complete futility of attempting to arrive at any justifiable conclusion. The physician, however, must not become

52. Drummond, J. C.; Noble, R. L., and Wright, M. D.: Studies on the Relationship of Vitamin E (Tocopherols) to the Endocrine System, *Endocrinology* 1: 275-286 (Nov.) 1939. Biddulph, C., and Meyer, R. K.: The Influence of Vitamin E-Deficiency on the Endocrine Glands of Rats, Particularly on the Gonadotropic Hormone Content of the Pituitary Gland, *Am. J. Physiol.* 133: 259-271 (Feb.) 1941.

53. The Treatment of Habitual Abortion with Vitamin E, Report of the Council on Pharmacy and Chemistry, *J. A. M. A.* 114: 2214-2218 (June 1) 1940. Evans, H. M.: The William Henry Welch Lectures: New Light on the Biological Role of Vitamin E, *J. Mt. Sinai Hosp.* 6: 233-244 (Jan.-Feb.) 1940.

iconoclastic but must keep an open mind on this subject and await results of further study.⁵⁴

Vitamin E has been used in the treatment of various other disturbances of the reproductive system, including male and female sterility, menstrual disturbances, toxemias of pregnancy, faulty lactation and vaginal pruritus. The reported results are at variance and cannot be accepted until further evidence has been accumulated.

Myoneurogenic Disturbances.—During the past two years clinicians have concerned themselves with the possible benefit of vitamin E in the treatment of various neuromuscular disturbances. The encouragement aroused by early reports⁵⁵ on the treatment of anyotrophic lateral sclerosis with vitamin E was short lived. More extensive studies soon followed and the results were discouraging⁵⁶ in treatment of both amyotrophic lateral sclerosis and various forms of dystrophy. Wechsler's reports,⁵⁷ however, continue to show favorable results in the treatment of anyotrophic lateral sclerosis. He suggested that the therapeutic doses

54. Widenbauer, F.: Versuche mit Weizenkeimöl (vitamin E) bei der Aufzucht von Frühgeburten, *Ztschr. f. Kinderh.* **60**: 216-221 (Oct. 15) 1938. Bacharach, A. L.: Vitamin E and Habitual Abortion, *Brit. M. J.* **1**: 890 (June 1) 1940. Mulherin, C. M.: Vitamin E in Obstetrics, *Bull. Univ. Hosp. Augusta, Ga.* **3**: 4-7 (March) 1941. Almquist, H. J., and Klose, A. A.: Comparative Activities of Certain Antihemorrhagic Compounds, *Proc. Soc. Exper. Biol. & Med.* **45**: 55-59 (Oct.) 1940.

55. Bicknell, Franklin: Vitamin E in the Treatment of Muscular Dystrophies and Nervous Diseases, *Lancet* **1**: 10-13 (Jan. 6) 1940. Wechsler, I. S.: Recovery in Amyotrophic Lateral Sclerosis Treated with Tocopherols (Vitamin E): Preliminary Report, *J. A. M. A.* **114**: 948-950 (March 16) 1940. Stone, Simon: Treatment of Muscular Dystrophies and Allied Conditions: Preliminary Report on Use of Vitamin E (Wheat Germ Oil), *ibid.* **114**: 2187-2191 (June 1) 1940.

56. Shelden, C. H.; Butt, H. R., and Woltman, H. W.: Vitamin E (Synthetic Alpha-Tocopherol) Therapy in Certain Neurologic Disorders, *Proc. Staff Meet., Mayo Clin.* **15**: 577-580 (Sept. 11) 1940. Doyle, A. M., and Merritt, H. H.: Vitamin Therapy of Diseases of the Neuro-muscular Apparatus, *Arch. Neurol. & Psychiat.* **45**: 672-679 (April) 1941. Denker, P. G., and Scheinman, Leonard: Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Alpha-Tocopherol), *J. A. M. A.* **116**: 1893-1895 (April 26) 1941. Ferrebee, J. W.; Klingman, W. O., and Frantz, A. M.: Vitamin E and Vitamin B₆; Clinical Experience in the Treatment of Muscular Dystrophy and Amyotrophic Lateral Sclerosis, *ibid.* **116**: 1895-1896 (April 26) 1941. McBryde, Angus, and Baker, L. D.: Vitamin Therapy in Progressive Muscular Dystrophy: Vitamin B₆, Other Factors of the B Complex, and Vitamin E, *J. Pediat.* **18**: 727-731 (June) 1941. Worster-Drought, C., and Shafar, J.: Motor Neurone Degeneration Treated with Vitamin E, *Lancet* **2**: 209-212 (Aug. 23) 1941. Harris, M. M.: Negative Therapeutic and Metabolic Effects of Synthetic Alpha-Tocopherol (Vitamin E) in Muscular Dystrophy, *Am. J. M. Sc.* **202**: 258-264 (Aug.) 1941. Fitzgerald, Gerald, and McArdle, Brian: Vitamins E and B₆ in the Treatment of Muscular Dystrophy and Motor Neurone Disease, *Brain* **64**: 19-42 (March) 1941.

57. Wechsler, I. S.: The Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Tocopherols), *Am. J. M. Sc.* **200**: 765-778 (Dec.) 1940. Wechsler, I. S.: Amyotrophic Lateral Sclerosis Treated with Synthetic Vitamin E, *Arch. Neurol. & Psychiat.* **45**: 873-875 (May) 1941.

previously used were too small and implied that 150 to 300 mg. given intramuscularly, and 200 mg. or more given by mouth, might be an adequate daily dose of alpha-tocopherol.

Since investigation in this field is relatively new, physicians must completely reserve their answer to the question "What can we expect of vitamin E in the treatment of human myoneurogenic disturbances?"

VITAMIN K

In the review of vitamins sponsored by the American Medical Association in 1939, vitamin K appeared under the section entitled "Other factors: less well known vitamins." This fact in itself emphasizes how rapid has been the increase in knowledge of this vitamin. In this brief review no attempt will be made to mention the large volume of literature which has accumulated on this subject during the past three years. For details and an extensive bibliography the reader is referred to recent monographs and reviews on the subject.⁵⁸

CHEMISTRY AND PHYSIOLOGY

Chemistry.—In May 1939 McKee and his associates reported the isolation of vitamin K₁ from alfalfa and of vitamin K₂ from putrefied fish meal and presented evidence to indicate a quinoid structure of these vitamins. Independently, several groups of investigators reported the structure of the vitamin K₁ molecule to be 2-methyl-3-phytyl-1,4-naphthoquinone. Vitamin K₂ has not yet been prepared synthetically, nor has its true structure been determined. Both vitamins are fat soluble, and exposure of the pure preparation to sunlight and artificial light results in a loss of the activity of the vitamin. The activity also is destroyed by alkalis and strong acids. Fieser and his associates have investigated nearly every possible modification of the vitamin K₁ molecule, and in every instance the change is attended with a distinct diminution in biologic potency.⁵⁹

Soon after it was demonstrated that vitamin K₁ and K₂ possessed a quinoid structure, other compounds

58. Butt, H. R., and Snell, A. M.: Vitamin K, Philadelphia, W. B. Saunders Company, 1941. Brinkhous, K. M.: Plasma Prothrombin; Vitamin K, *Medicine* **19**: 329-416 (Sept.) 1940. Bay, Ricardo: Hígado-protrombina-vitamina K: (estudio experimental y clínico), Buenos Aires, Univ., Inst. de Clin. Quir., Bol. **17**: 139-231 (Feb.-March) 1941. Koller, Fritz: Das Vitamins K und seine klinische Bedeutung, Leipzig, Georg Thieme, 1941.

59. Fieser, L. F.: The Chemistry of Vitamin K, *Ann. Int. Med.* **15**: 648-658 (Oct.) 1941.

possessing this structure were investigated. It was found that of all the compounds studied 2-methyl-1,4-naphthoquinone (menadione) proved to possess the strongest antihemorrhagic activity. By the chick assay method this compound has been found to be about three times as potent as vitamin K₁, at least on a basis of weight. Menadione is so active that several investigators have suggested that it be adopted as a basic standard assay of vitamin K. Because of the wide usefulness of this compound in clinical medicine, the Council on Pharmacy and Chemistry of the American Medical Association, on the recommendation of the Committee on Nomenclature, authorized menadione as a nonproprietary name for this substance.⁶⁰

Physiology.—Pure vitamin K₁ has not been available long enough to allow complete knowledge of its physiologic action to be collected. It has been suggested that vitamin K acts as a reversible oxidation reduction catalyst. It has been suggested that the reversible character of the vitamin may be used to explain the fact that small quantities are effective clinically. It is known, however, that the vitamin is associated in some way with the integrity of the hepatic parenchyma and with the metabolism of prothrombin.

The presence of adequate amounts of bile salts is required for proper absorption of vitamin K. Recently, it has been emphasized that excessive amounts of liquid petrolatum administered with meals may prevent proper absorption of this vitamin. Clinical experience with this vitamin indicates that it is not absorbed through the colon or upper part of the ileum but that it is absorbed readily through the upper part of the jejunum.

The vitamin apparently is not stored easily in the body, and clinical work indicates that what little is stored in the body is in the liver.

So far as is known, vitamin K is not present in the urine but it can be demonstrated in the feces. Whether it is there because organisms are present in the feces which are known to contain vitamin K or whether the presence of the vitamin in feces is referable to real excretion of vitamin K remains to be established.

So far as is known, vitamin K at present has no relation to immunity, infection, pregnancy, lactation or

60. Menadione, Nonproprietary Term for the Substance 2-Methyl-1,4-Naphthoquinone, Report of Council on Pharmacy and Chemistry, J. A. M. A. 116:1054 (March 15) 1941.

the nervousness associated with diseases of the gastrointestinal tract or cardiovascular system. It is associated intimately, however, with normal physiologic function of the liver and with proper coagulation of the blood. Its exact role in coagulation of blood is not known. Vitamin K is known to be necessary for proper formation of prothrombin, but in what manner this is accomplished remains to be determined. A deficiency of vitamin K from any cause produces a deficiency of prothrombin in the circulating blood, and in all instances, except those in which severe hepatic damage is present, this deficiency of prothrombin can be corrected by proper administration of vitamin K or synthetic compounds which possess antihemorrhagic activity.⁶¹

SOURCES, HUMAN REQUIREMENTS AND TOXICITY

Vitamin K is distributed widely in nature, and among its richest sources are green leaves of different kinds. Alfalfa and spinach are rich in the vitamin, and cabbage, cauliflower, carrot tops, soy bean oil and seaweed are all good sources. Less abundant sources are tomatoes, orange peel and hemp seed. Seeds, fruits and roots in general contain considerably less vitamin K than do green leaves of different kinds. Parts of the plant that contain chlorophyll usually have the largest amount of vitamin K. The vitamin also is found in a number of bacteria, and during growth of bacteria the vitamin apparently is synthesized and retained.⁶²

The exact minimal requirements of vitamin K for infant, child, mother or normal adult have not yet been determined. It has been suggested that the requirement of vitamin K for newborn infants is extremely low and that possibly 1 microgram of synthetic vitamin K is a sufficient daily amount. It has been pointed out that there is no relationship between the mother's diet and the postpartum level of prothrombin of newborn infants. Apparently a completely adequate diet for the pregnant woman, as it is understood today, is not sufficient to protect the child from the potential dangers of hemorrhage resulting from a deficiency of prothrombin. It is

61. Wilder, R. M.; Browne, H. C., and Butt, H. R.: *Diseases of Metabolism and Nutrition: Review of Certain Recent Contributions: I. Diseases of Metabolism; II. Nutrition*, Arch. Int. Med. **65**: 390-460 (Feb.) 1940. Butt, H. R., and Leary, W. V.: *Diseases of Nutrition: Review of Certain Recent Contributions*, Arch. Int. Med. **67**: 411-465 (Feb.) 1941. Butt, Leary and Wilder.¹²

known, however, that pure vitamin K₁ or a synthetic compound exhibiting vitamin K activity, in doses of from 1 to 2 mg., is capable of correcting deficiency of vitamin K in most instances. This dose, however, apparently depends on the degree of hepatic damage present. It is known that diarrhea and inadequate intestinal absorption will increase the need for vitamin K. This general lack of knowledge of requirements for vitamin K undoubtedly will be corrected as soon as methods are developed by which vitamin K can be measured in biologic material.

Toxicity.—To date no serious untoward reaction has been observed among persons who have received reasonable therapeutic doses of either natural concentrates of vitamin K, synthetic vitamin K₁ or any of the synthetic compounds exhibiting antihemorrhagic activity now available commercially. An effect has not been noted on blood pressure, respiration, permeability of capillaries or urinary excretion following administration of any of these compounds. It has been observed, however, that doses of menadione as large as 180 mg. administered orally to human beings result in vomiting and porphyrinuria. These huge doses, however, are so obviously greater than those employed for therapeutic use that at present it appears safe to continue therapeutic administration of these synthetic compounds. Fieser wisely pointed out that some clinical consideration should be given to the possible conflict or otherwise undesirable characteristics which may be associated with conjugates resulting from administration of menadione. He pointed out that the delayed action of the administered material would appear to be subject to considerable uncertainty, and the wide opportunity for transformation of different types would lead one to expect a variability in the response, depending on the manner of administration and the condition of the patient.⁶²

62. Molitor, Hans, and Robinson, H. J.: Oral and Parenteral Toxicity of Vitamin K₁, Phthiocol and 2-Methyl-1,4-Naphthoquinone, *Proc. Soc. Exper. Biol. & Med.* **43**:125-128 (Jan.) 1940. Shimkin, M. B.: Toxicity of Naphthoquinones with Vitamin K Activity in Mice, *J. Pharmacol. & Exper. Therap.* **71**:210-214 (March) 1941. Foster, R. H. K. (introduced by E. Chargoff with the technical assistance of H. H. Clark): Pharmacological Observations on Tetra-Sodium-2-Methyl-1,4-Naphthohydroquinone Diphosphoric Acid Ester, *Proc. Soc. Exper. Biol. & Med.* **45**:412-415 (Oct.) 1940. Stewart, J. D.: Oral and Parenteral Use of Synthetic Vitamin K-Active Substances in Hypoprothrombinemia, *Surgery* **3**:212-219 (Feb.) 1941.

METHODS FOR MEASURING DEFICIENCY OF VITAMIN K IN MAN: ASSAY METHODS, UNITAGE AND BIOLOGIC METHODS

Like every new vitamin, vitamin K possesses numerous methods of assay and standards of unity. For details of this subject two articles are referred to.⁶³ The wide interest in vitamin K and associated naphthoquinones has given rise to the need for convenient and accurate methods for their estimation. A step in this direction was made by Trenner and Bacher,⁶⁴ who described a method by which many quinone-like substances may be assayed. Others have also recently reported work in this direction.⁶⁵

Of clinical importance are the methods by which deficiency of vitamin K can be recognized by simple laboratory procedures. Several excellent methods for measuring deficiency of prothrombin in the blood of man have been described, but in the experience of many the method developed by Quick and his associates has been found adaptable for general use in the clinical laboratory. The method developed by Warner and his associates also is used with modification in many laboratories.⁶⁵ Details of these methods are given in several publications.⁶⁶

The so-called bedside method has received considerable use and is reported to be of great value for the general practitioner. Suitable compact sets for making this measurement at the bedside are now available commercially.⁶⁷ Several micromethods for measuring

63. Ansbacher, S.: Editorial Review: The Bioassay of Vitamin K, *J. Nutrition* **21**:1-12 (Jan.) 1941. Almquist, H. J.: Vitamin K, *Physiol. Rev.* **21**:194-216 (Jan.) 1941.

64. Trenner, N. R., and Bacher, F. A.: A Quantitative Reduction-Oxidation Method for the Estimation of Vitamin K₁ and Associated Quinones and Naphthoquinones, *J. Biol. Chem.* **137**:745-755 (Feb.) 1941.

65. Irreverre, Filadelfo, and Sullivan, M. X.: A Colorimetric Test for Vitamin K₁, *Science* **64**:497-498 (Nov. 21) 1941. Scudi, J. V., and Buhs, R. P.: A Colorimetric Oxidation-Reduction Method for the Determinations of the K Vitamins, *J. Biol. Chem.* **141**:451-464 (Nov.) 1941. Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: A Quantitative Study on Blood Clotting: Prothrombin Fluctuations Under Experimental Conditions, *Am. J. Physiol.* **114**:667-675 (Feb.) 1936.

66. Herbert, Freda K.: The Estimation of Prothrombin in Human Plasma, *Biochem. J.* **34**:1554-1568 (Dec.) 1940. Souter, A. W., and Kark, Robert: Quick's Prothrombin Test Simplified by the Use of a Stable Thromboplastin, *Am. J. M. Sc.* **200**:603-607 (Nov.) 1940. Quick, A. J.; Stanley-Brown, Margaret, and Bancroft, F. W.: A Study of the Coagulation Defect in Hemophilia and in Jaundice, *ibid.* **190**:501-511 (Oct.) 1935. Butt and Snell,⁶⁸ Brinkhous,⁶⁸ Bay,⁶⁸ Koller.⁶⁸

67. Ziffren, S. E.; Owen, C. A.; Hoffman, G. R., and Smith, H. P.: Control of Vitamin K Therapy: Compensatory Mechanism at Low Prothrombin Levels, *Proc. Soc. Exper. Biol. & Med.* **40**:595-597 (April) 1939.

deficiency of prothrombin of infants also have been described and are used in many institutions routinely.⁶⁸

It must be admitted that all current methods for the estimation of prothrombin are, of necessity, indirect. However, certain of these methods of measuring prothrombin are the most nearly accurate methods available at present for estimation of the tendency of a patient to bleed in the presence of suspected deficiency of prothrombin. The information afforded by the measurement of prothrombin in the circulating blood is much more nearly accurate in the prediction of the tendency of a patient to bleed than is the measurement of the coagulation of bleeding time as formerly used in the consideration of such tendencies.

CLINICAL USE OF VITAMIN K

Among Adults.—A number of conditions have been reported in which a deficiency of prothrombin exists that can be corrected by the administration of vitamin K.⁶⁹ Deficiency of prothrombin among human beings apparently may occur in any of the following circumstances:

1. After ingestion of a diet inadequate in vitamin K. This condition is rare but the clinical observation is well supported by the experimental production of low values for prothrombin in the blood of rabbits and mice following administration of diets deficient in vitamin K.

2. With inadequate intestinal absorption. This may result from (a) lack of bile in the intestine owing to decreased secretion of bile salts, (b) obstruction of the bile duct from any cause or (c) to inadequate absorption attributable to various intestinal lesions, such as intestinal obstruction, and to short-circuiting surgical

68. Kato, Katsuji: Microprothrombin Test with Capillary Whole Blood: A Modification of Quick's Quantitative Method, *Am. J. Clin. Path.* **10**: 147-153 (Feb.) 1940. Quick, A. J.: Determinations of Prothrombin, *Proc. Soc. Exper. Biol. & Med.* **42**: 788-789 (Dec.) 1939. Bray, W. E., and Kelley, O. R.: Prothrombin Studies, Especially in the Newborn, *Am. J. Clin. Path.* **10**: 154-167 (Feb.) 1940. Kelley, O. R., and Bray, W. E.: Prothrombin Time Determination, *J. Lab. & Clin. Med.* **25**: 527-530 (Feb.) 1940. Kato, Katsuji, and Poncher, H. G.: The Prothrombin in the Blood of Newborn Mature and Immature Infants as Determined by the Microprothrombin Test, *J. A. M. A.* **114**: 749-753 (March 2) 1940.

69. Kark, Robert, and Souter, A. W.: Hypoprothrombinaemia and Avitaminosis-K in Man, *Brit. M. J.* **2**: 190-194 (Aug. 9) 1941. Smith, H. P., and Owen, C. A.: Vitamin K: Its Use in Patients with Obstructive Jaundice or with Biliary Fistulas, *Rev. Gastroenterol.* **7**: 520-526 (Nov.-Dec.) 1940. Hicks, J. D.: A Review of the Literature Concerning Hemorrhage in Obstructive Jaundice; the Significance of Prothrombin and of Vitamin K Therapy, *M. J. Australia* **1**: 46-51 (Jan. 11) 1941.

procedures. It likewise has been demonstrated that severe diarrheal diseases, such as ulcerative colitis, sprue or celiac disease, may result in a deficiency of prothrombin.⁷⁰

3. Injury to the liver. There is, of course, considerable evidence, both clinical and experimental, to indicate that the liver plays an active part in the formation of prothrombin and that any severe injury to this organ results in a deficiency of prothrombin.⁷¹

The story of deficiency of prothrombin resulting from obstructive jaundice or from biliary fistula has been told so often that it needs no repetition here, but the group of cases in which there is inadequate absorptive surfaces of the intestine deserves some consideration. A deficiency of prothrombin as a cause of bleeding in cases of various intestinal disorders is something new in clinical medicine. Although instances of deficiency in prothrombin referable to the effect of intestinal disorders are not often encountered, they do comprise a rather distinct group and one which bears close observation. When patients who have extensive disease of the intestine, such as sprue, chronic ulcerative colitis, intestinal obstruction or ileitis, or who have had multiple short-circuiting operations on the intestinal tract experience hemorrhage either before or after surgical treatment, deficiency in prothrombin should be recognized and corrected before other forms of treatment are instituted. One of the most important points in handling these conditions is for the physician to follow the level of prothrombin in the blood closely before and after operation in all cases of abnormalities of intestinal mucosa, particularly in cases in which the postoperative condition requires continued aspiration of gas and secretions from the intestinal tract. This practice has solved the mystery of obscure intestinal bleeding which occurs frequently in such cases and definitely has reduced postoperative morbidity and mortality.

70. Sharp, E. A.; Konder Heide, E. C., and Good, W. H.: Vitamin K Activity of 2-Methyl-1,4-Naphthoquinone and 4-Amino-2-Methyl-1-Naphthol in Hypoprothrombinemia, *J. Lab. & Clin. Med.* **26**: 818-822 (Feb.) 1941. Kark, Robert; Souter, A. W., and Hayward, J. C.: A Hemorrhagic Diathesis in Idiopathic Steatorrhea: Observations on Its Association with Vitamin K Deficiency, *Quart. J. Med.* **9**: 247-261 (Oct.) 1940. Allen, J. G.: The Comparative Prothrombin Responses to Vitamin K and Several of Its Substitutes in a Case of Nontropical Sprue, *New England J. Med.* **224**: 195-197 (Jan. 30) 1941.

71. Butt, H. R.; Leary, W. V., and Wilder, R. M.: Diseases of Nutrition: Review of Certain Recent Contributions, *Arch. Int. Med.* **69**: 277-343 (Feb.) 1942.

It has been well demonstrated clinically that primary hepatic disease, such as cirrhosis, atrophy or chronic hepatitis, frequently is accompanied by deficiency of prothrombin. This deficiency of prothrombin is not the result of deficiency of vitamin K but apparently is the direct result of severe hepatic damage. Under these conditions the deficiency of prothrombin usually is not relieved by administration of vitamin K in any amount. It is well to recall that instances of severe hepatic damage occur in any disease in which the liver might be involved, and although this group of cases is somewhat small this possibility must be considered. It is true that frequently repeated doses of vitamin K are necessary in order to produce the desired effect, but when the usual therapeutic dose of vitamin K has been doubled or tripled without producing the desired effect it is fairly certain that, regardless of the amount of vitamin K administered, there will be no response to elevation of prothrombin in the circulating blood.

Regardless of the etiologic factors in the deficiency of prothrombin of man, treatment in most instances essentially is the same. In cases in which there is inadequate bile in the gastrointestinal tract natural vitamin K₁ or synthetic compounds exhibiting vitamin K activity which are given by mouth should be accompanied by administration of from 5 to 10 grains (0.3 to 0.65 Gm.) of bile salts. Synthetic compounds with vitamin K activity, now available on the market and given orally in doses of from 1 to 2 mg. daily, usually constitute an adequate dose. There also is available on the market a water soluble compound, 4-amino-2-methyl-1-naphthol hydrochloride, which can be given effectively by mouth without bile salts. This compound and other synthetic compounds also are available commercially for intravenous and intramuscular administration.⁷² Their action is rapid.⁷³ Daily

72. Olwin, J. H.: The Intravenous Use of Vitamin K, *J. A. M. A.* **117**: 432-435 (Aug. 9) 1941. Emmett, A. D.; Kamm, Oliver, and Sharp, E. A.: The Vitamin K Activity of 4-Amino-2-Methyl-1-Naphthol and 4-Amino-3-Methyl-1-Naphthol, *J. Biol. Chem.* **133**: 285-286 (March) 1940. Anderson, E. R.; Karabin, J. E.; Udesky, Herbert, and Seed, Lindon: Parenteral Administration of a Water-Soluble Compound with Vitamin K Activity: 4-Amino-2-Methyl-1-Naphthol Hydrochloride, *Arch. Surg.* **41**: 1244-1250 (Nov.) 1940.

73. Weir, J. F.; Butt, H. R., and Snell, A. M.: Further Observations on the Clinical Use of Vitamin K, *Am. J. Digest. Dis.* **11**: 485-490 (Nov.) 1940. Tocantins, L. M., and Jones, H. W.: Hypoprothrombinemia; Effect of Peroral and Parenteral Administration of a Synthetic Vitamin K Substitute (2-Methyl-1,4-Naphthoquinone), *Ann. Surg.* **113**: 276-283 (Feb.) 1941. Seligman, A. M.; Hurwitz, Alfred; Frank, H. A., and Davis, W. A.: The Intravenous Use of Synthetic Vitamin K₁, *Surg., Gynec. & Obst.* **73**: 686-701 (Nov.) 1941.

doses of from 1 to 2 mg. usually are sufficient parenterally. Most investigators interested in this subject suggest that prior to operation in any of these conditions, regardless of the concentration of prothrombin in the blood, vitamin K in some form should be given for from one to two days. After operation, the concentration of prothrombin in the blood should be followed carefully and vitamin K administered as necessary. In instances in which the level of prothrombin in the circulating blood is sharply decreased before operation, vitamin K should be administered routinely preoperatively and postoperatively for several days, and the concentration of prothrombin in the blood should be determined for at least eight to ten days thereafter.

Some workers⁷⁴ recently have felt that the change effected in a particular level of prothrombin by administration of vitamin K may provide some index as to the nature of the disease being treated, with particular reference to intrahepatic and extrahepatic jaundice. Data now at hand do not unequivocally establish this fact.

Deficiency of Prothrombin Among Newborn Infants.—It is agreed generally that during the first few days of an infant's life a deficiency of prothrombin exists in the circulating blood. The cause of this normal physiologic deficiency, however, is still controversial. Waddell and Guerry were the first to report the important discovery that this physiologic deficiency of prothrombin of newborn infants and the bleeding tendency which sometimes developed could be corrected by administration of vitamin K. Since that time numerous reports have appeared concerning the effect of the various compounds possessing vitamin K activity on the level of prothrombin of newborn infants and the effect of such compounds on the hemorrhage which frequently occurs. The important suggestion also has been made that the deficiency of prothrombin existing at the time of birth might account in many instances for the intracranial hemorrhages which sometimes follow protracted labor and which frequently result in permanent paralysis.

74. Allen, J. G., and Julian, O. C.: Response of Plasma Prothrombin to Vitamin K Substitute Therapy in Cases of Hepatic Disease, *Arch. Surg.* **41**: 1363-1365 (Dec.) 1940. Andrus, W. DeW.: The Newer Knowledge of Vitamin K, *Bull. New York Acad. Med.* **17**: 116-134 (Feb.) 1941. Kark, R., and Sauter, A. W.: The Response to Vitamin K: A Liver Function Test, *Lancet* **2**: 693-696 (Dec. 6) 1941.

It has been reported and well established by several groups of workers that administration of vitamin K to mothers prior to delivery will prevent the usual fall in the level of prothrombin in the blood which is observed among newborn infants and that administration of vitamin K to the newborn infant also will increase concentration of prothrombin in the plasma.⁷⁵

On the basis of work now available, it appears that 2 mg. of menadione given by mouth to a mother one half to forty-eight hours before delivery is effective in preventing hemorrhagic disease of the newborn infant.⁷⁶ There is good evidence to indicate that, although the feeding of vitamin K to the infant after birth increases the concentration of prothrombin, the concentrations in these instances are not as high as those achieved by antepartum administration of the vitamin to the mother.

Many workers believe that instances of cerebral hemorrhage occurring in the course of birth with minimal trauma are precipitated by small hemorrhages which endure for a number of days. For this reason many workers interested in this problem believe that the lives of some of the infants might be saved if the blood at birth exhibits better properties of coagulation. Most investigators believe that vitamin K given in some form should be administered to every mother at the onset of labor. Some still insist that the vitamin should also be given to the newborn infant as an added precaution. In any event, the plan is so simple, the vitamin so cheap and the toxic reactions so minimal that this program should be adopted universally in the hope of preventing injury at birth.

75. Lawson, R. B.: Treatment of Hypoprothrombinemia (Hemorrhagic Disease) of the Newborn Infant, *J. Pediat.* **18**: 224-234 (Feb.) 1941. Valentine, Eleanor H.; Reinhold, J. G., and Schneider, Erich: The Effectiveness of Prenatal Administration of 2-Methyl-1,4-Naphthoquinone in Maintaining Normal Prothrombin Levels in Infants, *Am. J. M. Sc.* **202**: 359-364 (Sept.) 1941. Ross, S. G., and Malloy, H. T.: Blood Prothrombin in the Newborn: The Effect of Vitamin K on the Blood Prothrombin and on Hemorrhagic Disease of the Newborn, *Canad. M. A. J.* **45**: 417-421 (Nov.) 1941.

76. Hellman, L. M., and Shettles, L. B.: The Prophylactic Use of Vitamin K in Obstetrics, *South. M. J.* **35**: 289-293 (March) 1942.

CHAPTER XI

THE WATER SOLUBLE VITAMINS

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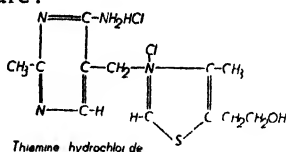
This group of dietary factors is classified as the water soluble vitamins because, like all vitamins, they are required by the body in extremely small amounts and because the individual chemical compounds are soluble in water although the degree of solubility may vary greatly from the sparingly soluble riboflavin to the readily soluble ascorbic acid. These are the only characteristics common to the individual components because their functions in the living cell may differ greatly and their chemical structures may vary from the simple configuration of nicotinic acid to the more complicated molecular structure of thiamine and riboflavin. Based largely on the source material used in early isolation work and the kind of experimental animal employed for the assay, the water soluble vitamins are generally subdivided into the B vitamins and vitamin C, together with related factors.

No attempt will be made to cover in this short summary the vast amount of literature which is accumulating on the water soluble vitamins. A symposium entitled "The Vitamins" published by the American Medical Association in 1939 includes a detailed survey of the facts known at that time. Therefore this chapter will include only a general summary of the more significant facts, and reference will be made to original papers only when they have been published within the past few years. Since this review will stress the nutritional aspects of these vitamins, the description of the clinical aspects of these deficiency diseases will of necessity be limited.

The B complex now is known to consist of at least a dozen separate factors, nine of which can be obtained in crystalline form. Each factor will be discussed separately and in more or less chronological order of its recognition and identification.

THIAMINE

Thiamine hydrochloride is a white crystalline substance readily soluble in water and possessing a nutlike and salty taste and a yeastlike odor. The empirical formula is $C_{12}H_{18}N_4O_2S_2Cl_2$ and the compound has the following structure:



It is rapidly destroyed in neutral or alkaline solutions because of hydrolytic cleavage into its constituent pyrimidine and thiazole rings, but in acid solutions it can be sterilized for half an hour at 120 C. without appreciable loss of activity. In the dry form the vitamin is very stable, and it is not readily destroyed by oxidation. Its activity is rapidly destroyed by sulfite, a fact which may explain the loss of thiamine during the sulfuring of fruits.

In foods and in tissues it occurs both in the free form and as thiamine pyrophosphate or cocarboxylase. In the latter form it functions in the living cell as a coenzyme in carbohydrate metabolism. In a thiamine deficiency the metabolism of carbohydrate is incomplete and pyruvic acid accumulates in the tissues, a condition which is used clinically in determining thiamine insufficiency. Many of the symptoms which have been observed in beriberi may be related to faulty carbohydrate metabolism, although it is still difficult to differentiate an uncomplicated thiamine deficiency from multiple deficiencies. Some of the nerve lesions which have been described in experimental animals suffering from polyneuritis are certainly related to a deficiency of riboflavin, but there is also good evidence that a lack of thiamine may directly cause neuropathologic changes.

The variety of symptoms seen in the human being has been summarized by Spies and Williams¹ and by Jolliffe.² Wilder³ has pointed out that the type of

1. Williams, R. R., and Spies, T. D.: *Vitamin B₁ and Its Use in Medicine*, New York, Macmillan Company, 1938.

2. Jolliffe, Norman: *Recent Advances in Clinical Applications of the B Vitamins*, *J. Am. Dietet. A.* **17**: 5 (Jan.) 1941.

3. Wilder, R. M.: *Nutritional Problems as Related to National Defense*, *Am. J. Digest. Dis.* **8**: 243 (July) 1941. Williams, R. D., and Mason, H. L.: *Further Observations on Induced Thiamine (Vitamin B₁) Deficiency and Thiamine Requirement of Man*, *Proc. Staff Meet., Mayo Clin.* **16**: 433 (July 9) 1941.

symptoms which develop depends to a considerable extent on the rate at which the deficiency develops, but in all cases the subjects become depressed, irritable, quarrelsome, uncooperative and fearful. An anemia of the hyperchronic type has also been described in a number of thiamine deficient patients.

Although the official method for the estimation of thiamine is the rat assay procedure described in the U. S. P. XI, 1939 Supplement, both the thiochrome and yeast fermentation methods are suitable for most foods. The latter methods have the advantage that they can be used for substances of low thiamine content. Only a few foods can be classified as rich sources of thiamine; they include peas, beans, oatmeal, whole wheat, lean pork and peanuts. However, one must not overlook the staple foods such as milk, vegetables and fruits, which may contribute appreciable amounts of thiamine in the diet although the amount per unit of weight is relatively low.

The Food and Nutrition Board of the National Research Council recommends 1.5 to 2.3 mg. as the daily thiamine allowance for the average adult man. The minimum daily requirement as established by the U. S. Food and Drug Administration is 1 mg. The requirement is increased in periods of active growth and during pregnancy and lactation. Pathologic conditions such as fevers and hyperthyroidism, in which there is a general increased metabolism, also increase the requirement. The effect of external temperature on the thiamine requirement of young rats has been reported by Mills,⁴ who found the need per unit of food to be twice as high at 91 F. as at 65 F. Mills⁵ also discusses the relation of these findings to the resistance of persons living in the tropics.

Diets high in fat have a definite sparing action on the requirement of thiamine in both rats and dogs. This is undoubtedly because fat metabolism does not require cocarboxylase. The human diet may rarely undergo sufficient change in fat content to alter materially the thiamine requirement. Cahill,⁶ studying the

4. Mills, C. A.: Vitamin and Protein Requirements at Different Temperatures, *Am. J. Physiol.* **133**: 390 (June) 1941.

5. Mills, C. A.: Environmental Temperatures and Thiamine Requirements, *Am. J. Physiol.* **133**: 525 (July) 1941.

6. Cahill, W. M.: Urinary Excretion of Thiamine on High Fat Diets, *J. Nutrition* **21**: 411 (April) 1941.

urinary excretion of thiamine in human subjects, could find no increase when part of the carbohydrate was replaced by fat.

In table 1 is presented the vitamin content of a few typical foods. It is evident that, aside from pork,

TABLE 1.—*Vitamin Content of a Few Typical Foods*

Milligrams per hundred grams (edible portion)					
Food	Thiamine	Ribo- flavin	Nico- tinic Acid	Panto- thenic Acid	Pyri- doxine
Apples	0.025	0.050	0.500	0.050
Bananas	0.040	0.080	0.600	0.070
Bread:					
white (unfortified) ...	0.070	0.100	0.800	0.400	0.300
white (fortified)	0.280	0.14	1.500	0.400	0.300
Cabbage	0.060	0.050	0.290	0.225	0.290
Carrots	0.050	0.100	1.500	0.210	0.190
Cheese	0.030	0.500	0.350
Cornmeal	0.200	0.150	1.500	0.800
Eggs	0.250	0.400	0.050	2.700
Meats:					
Beef	0.150	0.250	6.500	1.100	0.400
Pork (loin)	1.500	0.200	9.200	1.500	0.600
Poultry (light meat)	0.075	0.060	6.100	0.800
Poultry (dark meat)	0.100	0.250	7.300	2.000	0.200
Calf's liver	0.400	3.200	20.000	5.200
Pork liver	0.400	2.700	22.000	5.400
Milk (whole, fluid)	0.045	0.200	0.070	0.300	0.200
Oatmeal	0.800	0.160	1.130	1.300	0.250
Oranges	0.070	0.030	0.220	0.070
Peas (fresh)	0.300	0.190	0.750	0.600
Peanuts	0.800	0.300	13.000	3.400
Potatoes	0.125	0.060	1.160	0.400	0.160
Spinach	0.075	0.250	0.720	0.200
Tomatoes	0.050	0.050	0.580	0.075
Turnips	0.040	0.060	0.250
Yeast (brewers' dry)	12.000	4.000	40.000	20.000	5.500
Whole wheat	0.450	0.120	5.900	1.300	0.460

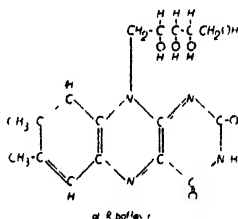
oatmeal, whole wheat, enriched bread and peas, at least five to ten servings (100 Gm.) of the individual foods must be consumed daily to meet the minimum daily requirement. Thus it is not a simple task to select a diet containing adequate thiamine without the use of whole grain cereals or enriched flour and bread. It is well known that significant amounts of thiamine may be lost during the preparation of foods because of the fact that the vitamin is readily soluble in water

and easily destroyed by moist heat. Under normal conditions there is probably little destruction of thiamine in the digestive tract, although intestinal disturbance may seriously retard the absorption of this vitamin.

Recently a factor destructive of vitamin B₁ has been found in raw fish. Green, Carlson and Evans⁷ observed a type of paralysis in foxes fed diets containing 20 per cent fresh carp and identified the condition as a thiamine avitaminosis analogous to Wernicke's disease. Further studies⁸ on the mechanism of inactivation point to an enzymatic destruction.

RIBOFLAVIN

Riboflavin is a practically odorless, orange-yellow crystalline compound which in water solution shows a characteristic yellow-green fluorescence. The empirical formula is C₁₇H₂₀N₄O₆ with the following structure:



This vitamin is rather heat stable, especially in acid mediums, but extremely labile when exposed to light. In nature riboflavin may occur as such, as riboflavin phosphate or as a constituent of specific flavoproteins. These flavoproteins function as important enzymes in tissue respiration. Enzymes known to contain riboflavin include cytochrome reductase, d-amino acid oxidase and xanthine oxidase.⁹ A definite reduction in the tissue concentration of the latter enzymes has been observed in riboflavin deficient animals.¹⁰ Aside from

7. Green, R. G.; Carlson, W. E., and Evans, C. A.: A Deficiency Disease in Foxes Produced by Feeding Fish, *J. Nutrition* **21**:243 (March) 1941.

8. Spitzer, E. H.; Coombes, A. I.; Elvehjem, C. A., and Wisnicky, W.: Inactivation of Vitamin B₁ by Raw Fish, *Proc. Soc. Exper. Biol. & Med.* **48**:376 (Oct.) 1941. Woolley, D. W.: Destruction of Thiamine by a Substance in Certain Fish, *J. Biol. Chem.* **141**:997 (Dec.) 1941.

9. Hogness, T. R.: A Symposium on Respiratory Enzymes, The University of Wisconsin Press, Madison, 1942, p. 134.

10. Axelrod, A. E., and Elvehjem, C. A.: The Xanthine Oxidase Content of Rat Liver in Riboflavin Deficiency, *J. Biol. Chem.* **140**:725 (Sept.) 1941.

retarded growth in young animals, other symptoms include dermatitis and cataract in rats and characteristic paralysis in chicks. A recent report by Baum, Michaelree and Brown¹¹ indicates that the incidence of cataract in rats is increased if the diet supplies a small amount (1 to 2 micrograms daily) of riboflavin. Phillips and Engel have shown a specific neuropathologic condition of the main peripheral nerve trunks in chicks on low riboflavin rations. Similar changes were not observed in the rat until the riboflavin deficiency was aggravated by an increased fat content of the diet.¹² Both acute and chronic riboflavin deficiency has been studied in dogs.¹³ On a diet very low in this vitamin a characteristic collapse syndrome and sudden death are observed in six to eight weeks. Prolonged subsistence on a diet low in riboflavin leads to neurologic abnormalities accompanied by myelin degeneration of peripheral nerves and the posterior columns of the spinal cord. Street, Cowgill and Zimmerman¹³ have shown that opacities of the cornea may occur in the dog as well as in the rat.

In man the symptoms include inflammation of the lips, fissures at the corners of the mouth, glossitis, dermatitis and vascularizing keratitis.¹⁴ The ocular symptoms first described by Sydenstricker and his co-workers¹⁵ appear to be very constant and may appear before other symptoms of the deficiency.

The riboflavin content of foods may be determined by measuring the growth response obtained in chicks or rats maintained on basal rations low in the vitamin, but the more rapid microbiologic method of Snell and Strong¹⁶ is now used rather extensively. Chemical methods involving measurement of fluorescence are also

11. Baum, H. M.; Michaelree, J. F., and Brown, E. B.: The Quantitative Relationship of Riboflavin to Cataract Formation in Rats, *Science* **95**: 24 (Jan. 2) 1942.

12. Shaw, J. H., and Phillips, P. H.: The Pathology of Riboflavin Deficiency in the Rat, *J. Nutrition* **22**: 345 (Oct.) 1941.

13. Street, H. R.; Cowgill, G. R., and Zimmerman, H. M.: Further Observations of Riboflavin Deficiency in the Dog, *J. Nutrition* **22**: 7 (July) 1941.

14. Sebrell, W. H., and Butler, R. E.: Riboflavin Deficiency in Man, *Public Health Rep.* **53**: 2282 (Dec. 30) 1938. Sydenstricker, V. P.; Geeslin, L. E.; Templeton, C. M., and Weaver, I. W.: Riboflavin Deficiency in Human Subjects, *J. A. M. A.* **113**: 1697 (Nov. 4) 1939.

15. Sydenstricker, V. P.; Sebrell, W. H.; Cleckley, H. M., and Kruse, H. D.: The Ocular Manifestations of Ariboflavinosis: A Progress Note, *J. A. M. A.* **114**: 2437 (June 22) 1940.

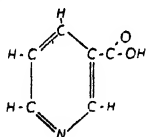
16. Snell, E. E., and Strong, F. M.: A Microbiological Assay for Riboflavin, *Indust. & Engin. Chem., Anal. Ed.* **11**: 346 (June) 1939.

being used.¹⁷ Riboflavin is widely distributed in plant and animal materials. Liver, milk and vegetables may be considered the best and most reliable sources in the human dietary. Seeds, which are so important as a source of thiamine, are poor sources of riboflavin.

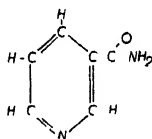
The Food and Nutrition Board recommends 2.2 to 3.3 mg. of riboflavin as the daily allowance for adult males, and the Food and Drug Administration has accepted 2 mg. a day as the minimum daily requirement. The limited values in table 1 show that one serving of liver will adequately meet the daily allowance, that 1 quart of milk will supply the minimum requirement, and that one serving of cheese or eggs will supply one fourth of the daily requirement. Sure and Dichek¹⁸ have demonstrated, in the case of rats, that riboflavin has a pronounced beneficial effect on the economy of food utilization for the synthesis of body tissues. In this connection it is interesting to note that Murlin¹⁹ reports the biologic value of proteins in bread is improved in the presence of extra B vitamins.

NICOTINIC ACID

Nicotinic acid occurs as white, needle-like crystals, is nonhygroscopic and stable in air and has the empirical formula $C_6H_5O_2N$. The structural formula of both the acid and the physiologically active amide are shown.



Nicotinic acid
(Niacin)



Nicotinic acid amide
(Niacin amide)

The sensation of flushing and erythema of the skin which is often observed on administration of nicotinic acid is not produced by nicotinic acid amide. Nicotinic acid is a comparatively weak acid, and its alkaline salts

17. Hodson, A. Z., and Norris, L. C.: A Fluorometric Method for Determining the Riboflavin Content of Foodstuffs, *J. Biol. Chem.* **131**: 621 (Dec.) 1939. Conner, R. T., and Straub, G. J.: Combined Determination of Riboflavin and Thiamine in Food Products, *Indust. & Engin. Chem., Anal. Ed.* **13**: 385 (June) 1941.

18. Sure, Barnett, and Dichek, Maurice: Riboflavin as a Factor in Economy of Food Utilization, *J. Nutrition* **21**: 453 (May) 1941.

19. Murlin, J. R.; Marshall, Margaret E., and Kochakian, C. D.: Digestibility and Biological Value of Whole Wheat Breads as Compared with White Bread, *J. Nutrition* **23**: 573 (Dec.) 1941.

in solution show a slightly alkaline reaction. It is stable to autoclaving temperatures when in solution and shows no loss of activity when exposed to dry heat. Owing to numerous objections to the term nicotinic acid, niacin and niacin amide have been proposed as unobjectionable synonyms for the acid and amide.

In the body nicotinic acid functions as a component of two important coenzymes, coenzyme I or cozymase and coenzyme II, which are concerned in both glycolysis and respiration.²⁰ The structure of the two coenzymes is very similar, differing only in the number of phosphoric acid units. Coenzyme I is a diphosphopyridine nucleotide, and coenzyme II is a triphosphopyridine nucleotide. In nicotinic acid deficiency it is possible to demonstrate a decreased cozymase content of the liver and muscle tissue. There has been some question about the cozymase content of the blood during deficiency, but all workers²¹ are now agreed that the change if demonstrable is very slight. It is thus impossible to use this method in the diagnosis of nicotinic acid deficiency.

The dog, pig and monkey are the only experimental animals that show typical nicotinic acid deficiency. Blacktongue in the dog was first described by Chittenden and Underhill, and in 1922 Goldberger and his co-workers concluded that blacktongue in dogs was analogous to human pellagra. The early symptoms of pellagra are weakness, lassitude, anorexia and indigestion, followed by sore and ulcerated mouth and diarrhea. The typical dermatitis usually simplifies the diagnosis. A more detailed summary of the symptoms has recently been made by Harris²² and by Youmans.²³ Spies, Walker and Woods²⁴ have shown that infants and children also suffer from nicotinic acid deficiency in areas where pellagra is endemic, although typical lesions

20. Elvehjem, C. A.: Relation of Nicotinic Acid to Pellagra, *Physiol. Rev.* **20**: 249 (April) 1940.

21. Kohn, H. I.; Klein, J. R., and Dann, W. J.: The V Factor Content and Oxygen Consumption of Tissues from the Normal and Blacktongue Dog, *Biochem. J.* **33**: 1432 (Sept.) 1939. Axelrod, A. E.; Spies, T. D., and Elvehjem, C. A.: The Effect of a Nicotinic Acid Deficiency upon the Coenzyme I Content of the Human Erythrocyte and Muscle, *J. Biol. Chem.* **133**: 667 (April) 1941.

22. Harris, Seale: Clinical Pellagra, St. Louis, C. V. Mosby Company, 1941.

23. Youmans, J. B.: Nutritional Deficiencies, Philadelphia, J. B. Lippincott Company, 1941.

24. Spies, T. D.; Walker, A. A., and Woods, A. W.: Pellagra in Infancy and Childhood, *J. A. M. A.* **113**: 1481 (Oct. 14) 1939.

are seldom seen in early infancy. Nicotinic acid is now widely used in the treatment of pellagra, but its use is most successful in conjunction with other vitamins and specific natural foods.

The activity of various compounds related in structure to nicotinic acid was investigated by Woolley and his co-workers,²⁵ and it was concluded that only those compounds which may undergo oxidation or hydrolytic conversion to nicotinic acid are active in the dog. Since that time some activity has been observed in human beings with quinolinic acid, pyrazine 2,3 dicarboxylic acid and pyrazine monocarboxylic acid. A recent paper by Dann, Kohn and Handler²⁶ summarizes much of the work on these compounds, and from their results as well as results in this laboratory one may conclude that the activity of these compounds is greatly inferior to that of nicotinic acid.

Since nicotinic acid is not required preformed in the diets of chicks or rats, the dog, originally used by Goldberger and his co-workers for the assay of the antipellagra potency of foods, is the only animal that can be used with any success. Fairly accurate values can be obtained by comparing the growth response obtained by feeding a definite weight of the food with that obtained after giving a standard dose of nicotinic acid.²⁷ Chemical methods may be used on many foods, and an improved method has recently been described by Dann and Handler.²⁸ A convenient method and one which I have found satisfactory is the microbiologic method of Snell and Wright.²⁹ In general there is good agreement between the results obtained with the three methods except in the case of liver and kidney. The values obtained with the dog assay for these materials are somewhat higher than the values obtained by the chemical or microbiologic methods. The best

25. Woolley, D. W.; Strong, F. M.; Madden, R. J., and Elvehjem, C. A.: Antiblacktongue Activity of Various Pyridine Derivatives, *J. Biol. Chem.* **124**: 715 (Aug.) 1938.

26. Dann, W. J.; Kohn, H. I., and Handler, Philip: The Effect of Pyrazine Acids and Quinolinic Acid on the V-Factor Content of Human Blood and on Canine Blacktongue, *J. Nutrition* **30**: 477 (Nov.) 1940.

27. Waisman, H. A.; Mickelsen, Olaf; McKibbin, J. M., and Elvehjem, C. A.: Nicotinic Acid Potency of Food Materials and Certain Chemical Compounds, *J. Nutrition* **19**: 483 (May) 1940.

28. Dann, W. J., and Handler, Philip: The Quantitative Estimation of Nicotinic Acid in Animal Tissues, *J. Biol. Chem.* **140**: 201 (July) 1941.

29. Snell, E. E., and Wright, L. D.: A Microbiological Method for the Determination of Nicotinic Acid, *J. Biol. Chem.* **139**: 611 (June) 1941.

sources of nicotinic acid include liver, yeast, lean meats and to a lesser extent peanuts, potatoes and vegetables.

It is difficult to establish an exact value for the nicotinic acid requirement of human beings. Balance experiments are complicated by the fact that excess nicotinic acid ingested is excreted not only as nicotinic acid but also as trigonelline and nicotinuric acid.³⁰ The Food and Nutrition Board has suggested 15 to 20 mg. as the daily allowance for an adult man, and the minimum requirement has been set at 10 mg. a day.

One may readily ascertain from table 1 why pellagra will develop on diets high in cornmeal and patent flour. These materials contain 1 to 1.5 mg. per hundred grams, and one would have to consume 1,000 Gm. to meet the minimum requirement, which is, of course, impossible. In contrast to corn, wheat contains 5 to 7 mg. per hundred grams and would be a reliable source of nicotinic acid if 80 to 90 per cent of the nicotinic acid were not removed during the milling process.³¹ Whole oats is also low in nicotinic acid, but barley is somewhat higher. One serving of liver will supply the daily allowance, and one serving of lean meat will supply about one half of the daily requirement. One hundred Gm. of peanuts will supply the requirement. Since nicotinic acid is a very stable compound there is little destruction during cooking, and the loss is negligible unless the cooking water is discarded.

PYRIDOXINE—VITAMIN B₆

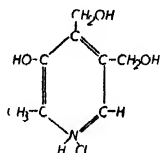
The early work on the isolation of vitamin B₆ was described in *The Vitamins* in 1939. Since that time the synthesis of pyridoxine has been described by Harris and Folkers³² and it, like thiamine, riboflavin and nicotinic acid, is available in the synthetic form on a commercial basis. Pyridoxine hydrochloride is a white crystalline powder, slightly bitter in taste and odorless, possessing the empirical formula $C_8H_{12}O_3NCl$. It is

30. Perlzweig, W. A.; Levy, E. D., and Sarett, H. D.: Nicotinic Acid Derivatives in Human Urine and Their Determination, *J. Biol. Chem.* **136**: 729 (Dec.) 1940. Melnick, Daniel; Robinson, W. D., and Field, Henry, Jr.: Influence of the Excretion of Other Pyridine Compounds on the Interpretation of the Urinary Nicotinic Acid Values, *J. Biol. Chem.* **136**: 131 (Oct.) 1940.

31. Tepley, L. J.; Strong, F. M., and Elvehjem, C. A.: The Distribution of Nicotinic Acid in Foods, *J. Nutrition* **23**: 417 (April) 1942.

32. Harris, S. A., and Folkers, Karl: Synthesis of Vitamin B₆, *J. Am. Chem. Soc.* **61**: 1245 (May) 1939.

separate and distinct from nicotinic acid, although the basic structure in both vitamins is the pyridine ring. The complete structure is



Pyridoxine hydrochloride

The mechanism in which vitamin B₆ functions in the living organism is unknown. It, like the previous vitamins discussed, may be related to enzyme systems, but there is no evidence for such a conclusion except the fact that it is rather closely bound to protein. There appears to be a functional relationship between unsaturated fatty acids and the vitamin.³³ McHenry and Gavin³⁴ suggest that pyridoxine brings about synthesis of fat from protein, but the nature of the mechanism is unknown.

Pyridoxine has been shown to be essential in the nutrition of the rat,³⁵ the chick,³⁶ the dog³⁷ and the pig.³⁸ An acrodynia characterized by edema, swelling and denuding of the paws and areas around the mouth and frequent thickening of the ears is associated with pyridoxine deficiency in the rat,³⁹ although it has been demonstrated⁴⁰ that a lack of this vitamin may cause

33. Birch, T. W.: The Relation Between Vitamin B₆ and the Unsaturated Fatty Acid Factor, *J. Biol. Chem.* **124**: 775 (Aug.) 1938.

34. McHenry, E. W., and Gavin, Gertrude: The B Vitamins and Fat Metabolism. IV. The Synthesis of Fat from Protein, *J. Biol. Chem.* **138**: 471 (April) 1941.

35. György, Paul; Sullivan, M., and Karsner, H. T.: Nutritional Dermatoses in Rats, *Proc. Soc. Exper. Biol. & Med.* **37**: 313 (Nov.) 1937.

36. Hegsted, D. M.; Oleson, J. J.; Elvehjem, C. A., and Hart, E. B.: The "Cartilage Growth Factor" and Vitamin B₆ in the Nutrition of Chicks, *J. Biol. Chem.* **130**: 423 (Sept.) 1939.

37. Fouts, P. J.; Helmer, O. M.; Lepkovsky, S., and Jukes, T. H.: Production of Microcytic Hypochromic Anemia in Puppies on Synthetic Diet Deficient in Rat Antidermatitis Factor (Vitamin B₆), *J. Nutrition* **16**: 197 (Aug.) 1938.

38. Chick, Harriette; Macrae, T. F.; Martin, H. J. P., and Martin, C. J.: The Water Soluble B Vitamins Other Than Aneurin (Vitamin B₁), Riboflavin and Nicotinic Acid Required by the Pig, *Biochem. J.* **32**: 2207 (Dec.) 1938.

39. György, Paul, and Eckardt, R. E.: Further Investigations on Vitamin B₆ and Related Factors of the Vitamin B₆ Complex in Rats, *Biochem. J.* **34**: 1143 (Sept.) 1940.

40. Conger, T. W., and Elvehjem, C. A.: The Biological Estimation of Pyridoxine (Vitamin B₆), *J. Biol. Chem.* **138**: 555 (April) 1941.

retarded growth without the dermatitis. The microcytic hypochromic anemia in dogs resulting from pyridoxine deficiency reported by Fouts and his co-workers³⁷ has been amply confirmed.⁴¹

No clear cut symptoms resulting from pyridoxine deficiency have been described in man. Spies, Bean and Ashe⁴² have reported an additional improvement in pellagrins by giving pyridoxine after treatment with nicotinic acid, riboflavin and thiamine. Smith and Martin⁴³ observed a rapid and satisfactory healing of the typical lesions of cheilitis with vitamin B₆ therapy. Although clinical treatment of such conditions as Parkinson's disease, muscular dystrophy and paralysis agitans has been studied, the results are not definite enough to permit postulation of the action of the vitamin or to associate any one of these syndromes with specific lack of pyridoxine in the diet. The human requirement is unknown, but animal experiments indicate that the vitamin B₆ requirement may be about the same as for thiamine; namely, about 2 mg. a day.

The most reliable method for determining the pyridoxine content of foods is probably the rat assay method.⁴⁰ Scudi⁴⁴ and Swaminathan⁴⁵ have used chemical methods. Among the best sources are rice bran, liver, yeast, cereals, legumes and milk. Whole wheat contains about 0.46 mg. per hundred grams, most meats 0.4 to 0.7 mg. per hundred grams on the fresh basis,⁴⁶ fresh vegetables about 0.1 mg. per hundred grams and milk about 2 mg. per quart (liter). Swaminathan⁴⁷ found diets consumed in India to supply 3.5 to 5 mg. a day.

41. Street, H. R.; Cowgill, G. R., and Zimmerman, H. M.: Some Observations of Vitamin B₆ Deficiency in the Dog, *J. Nutrition* **21**: 275 (March) 1941. McKibbin, J. M.; Schaefer, A. E.; Frost, D. V., and Elvehjem, C. A.: Studies on Anemia in Dogs Due to Pyridoxine Deficiency, *J. Biol. Chem.* **143**: 77 (Jan.) 1942.

42. Spies, T. D.; Bean, W. B., and Ashe, W. F.: A Note on the Use of Vitamin B₆ in Human Nutrition, *J. A. M. A.* **113**: 2414 (June 10) 1939.

43. Smith, Susan Gower, and Martin, D. W.: Cheilosis Successfully Treated with Synthetic Vitamin B₆, *Proc. Soc. Exper. Biol. & Med.* **43**: 660 (April) 1940.

44. Scudi, J. V.: On the Colorimetric Determination of Vitamin B₆, *J. Biol. Chem.* **139**: 707 (June) 1941.

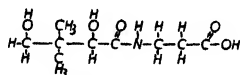
45. Swaminathan, M.: A Chemical Test for Vitamin B₆ in Foods, *Indian J. M. Res.* **28**: 427 (Oct.) 1940.

46. Henderson, L. M.; Waisman, H. A., and Elvehjem, C. A.: The Distribution of Pyridoxine (Vitamin B₆) in Meat and Meat Products, *J. Nutrition* **21**: 589 (June) 1941.

47. Swaminathan, M.: A Method for the Estimation of Vitamin B₆ in Urine, *Indian J. M. Res.* **29**: 561 (July) 1941.

PANTOTHENIC ACID

In 1939 the term "filtrate factor" was still used to designate that member of the B complex which prevented dermatitis in chicks. Although the so-called filtrate fractions prepared from liver extract were effective in the prevention of blacktongue in dogs, pellagra in human beings and dermatitis in chicks, it was demonstrated as soon as nicotinic acid was accepted as the antipellagra factor that the activity of these fractions in the prevention of chick dermatitis was not due to the nicotinic acid present but to a separate and distinct vitamin. Shortly thereafter Woolley, Waisman and Elvehjem⁴⁸ and Jukes⁴⁹ independently demonstrated that pantothenic acid, which Williams⁵⁰ had shown to be a growth factor for yeast as early as 1933, was similar to the chick antidermatitis factor. The complete synthesis of pantothenic acid was achieved in 1940.⁵¹ The vitamin is now available as the dextro-rotatory calcium salt, which occurs in fine dense white crystals that are odorless and slightly bitter in taste. The empirical formula is $(C_9H_{10}NO_5)_2Ca$. The structural formula for the free acid is:



Pantothenic acid

Pantothenic acid is fairly stable to moist heat, especially at a neutral p_H , but is destroyed by prolonged dry heat. The compound is readily hydrolyzed into the two component parts in alkaline solution. The compound is widely distributed in nature, but its function in normal metabolism is not known. It does occur in bound form in many tissues, since proteolytic enzymes are needed in order to liberate the compound completely from animal tissues.

Rats placed on diets low in pantothenic acid grow very poorly and develop in a few weeks necrosis of

48. Woolley, D. W.; Waisman, H. A., and Elvehjem, C. A.: Nature and Partial Synthesis of the Chick Antidermatitis Factor, *J. Am. Chem. Soc.* **61**: 977 (April) 1939.

49. Jukes, T. H.: Pantothenic Acid and the Filtrate (Chick Antidermatitis) Factor, *J. Am. Chem. Soc.* **61**: 975 (April) 1939.

50. Williams, R. J.; Lyman, C. M.; Goodyear, G. H.; Truesdail, J. H., and Haladay, D.: "Pantothenic Acid" a Growth Determinant of Universal Biological Occurrence, *J. Am. Chem. Soc.* **55**: 2912 (July) 1933.

51. Stiller, E. T.; Harris, S. A.; Finkelstein, Jacob; Keresztesy, J. C., and Folkers, Karl: Pantothenic Acid: VIII. The Total Synthesis of Pure Pantothenic Acid, *J. Am. Chem. Soc.* **62**: 1785 (July) 1940.

the adrenal cortex, which was first described by Daft and Sebrell.⁵² Changes in hair pigmentation (graying) have been observed in many laboratories when black or piebald rats are used. Unna, Richards and Sampson⁵³ have published reproductions of photographs illustrating these fur changes in nutritional achromotrichia. Schaefer, McKibbin and Elvehjem⁵⁴ have produced acute pantothenic acid deficiencies in dogs that are characterized by sudden collapse associated with decreased blood dextrose, increased nonprotein nitrogen and lowered blood chlorides. Severe intussusception in the intestinal tract and fatty livers have also been observed. Phillips and Engel⁵⁵ have reported specific neuropathologic changes of the spinal cord in chicks suffering from pantothenic acid deficiency. Wintrobe⁵⁶ has also found neuropathologic changes in pigs on synthetic diets low in pantothenic acid and other members of the B complex.

In spite of these interesting symptoms in experimental animals, little is known about the real significance of pantothenic acid in human nutrition. Spies and his co-workers⁵⁷ conclude from studies based largely on blood pantothenic acid values that pantothenic acid is essential to human nutrition. Krahne and Gordon⁵⁸ have studied the excretion of pantothenic acid in persons on different levels of intake. However, no specific symptoms in man have been correlated with a deficiency of the vitamin. This may be due to the fact that pantothenic acid is widely distributed and that even restricted diets may not be low enough to cause a serious deficiency.

52. Daft and Sebrell, cited by Daft, F. S.; Sebrell, W. H.; Babcock, S. H., Jr., and Jukes, T. H.: Effect of Synthetic Pantothenic Acid on Adrenal Hemorrhage, Atrophy and Necrosis in Rats, *Pub. Health Rep.* **55**: 1333 (July 26) 1940.

53. Unna, Klaus; Richards, Grace V., and Sampson, W. L.: Studies on Nutritional Achromotrichia in Rats, *J. Nutrition* **22**: 553 (Dec.) 1941.

54. Schaefer, A. E.; McKibbin, J. M., and Elvehjem, C. A.: Pantothenic Acid Deficiency Studies in Dogs, *J. Biol. Chem.* **143**: 321 (April) 1942.

55. Phillips, P. H., and Engel, R. W.: Some Histopathologic Observations on Chicks Deficient in the Chick Antidermatitis Factor or Pantothenic Acid, *J. Nutrition* **18**: 227 (Sept.) 1939.

56. Wintrobe, M. M.; Miller, J. L., Jr., and Lisco, Hermann: The Relation of Diet to the Occurrence of Ataxia and Degeneration of the Nervous System of Pigs, *Bull. Johns Hopkins Hosp.* **67**: 377 (Dec.) 1940.

57. Spies, T. D.; Stanbery, S. R.; Williams, R. J.; Jukes, T. H., and Babcock, S. H., Jr.: Pantothenic Acid in Human Nutrition, *J. A. M. A.* **115**: 523 (Aug. 17) 1940.

58. Krahne, H. F., and Gordon, E. S.: Pantothenic Acid in Human Nutrition, *J. Clin. Investigation*, to be published.

No figures can be given for the daily human requirement. The relatively high amount of pantothenic acid needed to produce good growth in rats on synthetic diets has led to the assumption that the requirement is considerably higher than that of some of the other B vitamins. However, work in this laboratory indicates that the requirement for dogs can be satisfied with 0.10 mg. per hundred grams ration, a level very similar to that of thiamine and riboflavin. According to these results the human requirement may not be far from 5 mg. a day.

The pantothenic acid content of foods may be measured by growth experiments with chicks, but the microbiologic methods⁵⁹ are now in more general use. Liver is one of the richest natural sources, and if 5 mg. is accepted as the daily requirement 100 Gm. of the fresh liver will meet this requirement. Meats, cereals and milk are all reliable sources. Few studies have been made on the loss of this vitamin during cooking, but the loss may be very similar to that for thiamine, since pantothenic acid is readily soluble in water and not too stable at elevated temperatures. Evidence is available to show that only about one half of the pantothenic acid in whole wheat is lost during the milling process.

CHOLINE

Choline is a colorless viscous fluid, and the more familiar choline chloride is a very hygroscopic white crystalline substance with a salty bitter taste. As expected from its chemical constitution, the compound is not stable to alkali treatment but is stable to acids even at elevated temperatures.

Choline has been recognized for many years as a component part of the phospholipid lecithin, but its functional importance in nutrition was not apparent until Best almost ten years ago demonstrated its role in the prevention of fatty livers in depancreatized dogs.⁶⁰ Choline is now considered an important mem-

59. Pennington, D.; Snell, E. E., and Williams, R. J.: *An Assay Method for Pantothenic Acid*, J. Biol. Chem. **135**: 213 (Aug.) 1940. Pelzar, M. J., Jr., and Porter, J. R.: *A Microbiological Assay Technic for Pantothenic Acid with the Use of Proteus Morganii*, *ibid.* **139**: 111 (May) 1941. Strong, F. M.; Feeney, R. E., and Earle, A.: *Microbiological Assay for Pantothenic Acid*, *Indust. & Engin. Chem., Anal. Ed.* **13**: 566 (Aug.) 1941.

60. McHenry, E. W.: *Choline, the B Vitamins and Fat Metabolism*, *Biological Symposia*, edited by H. B. Lewis, Lancaster, Pa., Jaques Cattell Press **5**: 177, 1941.

ber of the B complex, although Jacobi, Baumann and Meek⁶¹ have demonstrated that synthesis of this substance may occur in the rat.

The function of choline is in some way related to the mobilization of fatty acids in the body, since in its absence liver fat rapidly accumulates. Experiments with the dog and the rat have demonstrated that neutral fat was involved, since fatty livers in rats induced by feeding high cholesterol diets did not respond to choline treatment. The observations of du Vigneaud and his collaborators⁶² that the methyl groups of choline as well as those of methionine and betaine are transferable in the animal organism has led to the postulation that one of the functions of choline is to supply labile methyl groups. McHenry⁶⁰ states that there is evidence now that choline may function in at least three ways: to stimulate the formation of phospholipids, to make possible the production of acetyl choline or to supply labile methyl groups.

Jukes⁶³ has shown that choline is one of the factors required in addition to adequate manganese to prevent slipped tendon in young turkeys. Sure⁶⁴ reports that choline is indispensable for lactation in adults rats and in the prevention of paralysis in suckling rats. Depression of the growth rate when choline is omitted from the diet has been observed in the case of the rat by Richardson, Hogan, Long and Itschner,⁶⁵ in the chick by Hegsted, Mills, Elvehjem and Hart⁶⁶ and in the dog by Schaefer, McKibbin and Elvehjem.⁶⁷

61. Jacobi, H. P.; Baumann, C. A., and Meek, W. J.: The Choline Content of Rats on Various Choline Free Diets, *J. Biol. Chem.* **138**: 571 (April) 1941.

62. du Vigneaud, Vincent; Chandler, J. P.; Moyer, A. W., and Keppel, Dorothy M.: The Effect of Choline on the Ability of Homocystine to Replace Methionine in the Diet, *J. Biol. Chem.* **131**: 57 (Nov.) 1939. du Vigneaud, Vincent: The Interrelationship Between Choline and Other Methylated Compounds, *Biological Symposia* edited by H. B. Lewis, Lancaster, Pa., Jaques Cattrell Press **5**: 234, 1941.

63. Jukes, T. H.: Prevention of Perosis by Choline, *J. Biol. Chem.* **134**: 789 (July) 1940.

64. Sure, Barnett: The Essential Nature of Choline for Lactation and Growth of the Albino Rat, *J. Nutrition* **10**: 71 (Jan.) 1940.

65. Richardson, L. R.; Hogan, A. G.; Long, Barbara, and Itschner, K. I.: The Number of Vitamins Required by the Rat, *Proc. Soc. Exper. Biol. & Med.* **40**: 530 (April) 1941.

66. Hegsted, D. M.; Mills, R. C.; Elvehjem, C. A., and Hart, E. B.: Choline in the Nutrition of Chicks, *J. Biol. Chem.* **138**: 459 (April) 1941.

67. Schaefer, A. E.; McKibbin, J. M., and Elvehjem, C. A.: Importance of Choline in Synthetic Rations for Dogs, *Proc. Soc. Exper. Biol. & Med.* **47**: 365 (June) 1941.

The high requirement of the young rat for choline has been stressed by Griffith,⁶⁸ who previously reported fatty degeneration of the liver, hemorrhagic renal lesions, ocular hemorrhages and regression of the thymus within ten days after the rats had been placed on a choline low but otherwise adequate diet. These results on weanling rats are of special significance in the light of recent findings reported from India⁶⁹ that in 20 to 30 cases prematurely born infants showed definite fatty livers and hemorrhagic kidneys.

Choline forms insoluble compounds with Reinecke's salt, rhodozanic acid and mercury and can be determined chemically by these procedures. Griffith has studied the choline requirement of the weanling rat and finds that under his dietary conditions 4 to 6 mg. daily will give protection against fatty livers. By determining the level of test substance necessary to furnish similar protection, a measure of its choline content can be obtained. It is to be remembered that other substances which can furnish labile methyl groups such as betaine and sarcosine can function in a manner similar to choline.

As stated previously, lecithin contains choline, and thus meats, cereals, vegetables and eggs would be considered good sources of choline. Yeast seems to be extremely variable in its content of choline, some yeasts being almost free from the factor and others containing enough to protect against fatty livers when fed at 10 per cent of the ration.

Clinical work on choline is of course very limited, and no conclusions can be made until more extensive studies are carried out. Dr. P. G. Danis reported before the Southern Medical Association at St. Louis in November 1941 that choline was of some value in controlling icterus gravis in infants.

BIOTIN

Although biotin has been recognized as necessary for the growth of micro-organisms for some time, its significance in the nutrition of animals is just in the process of being elucidated. Biotin was first isolated in 1936 by Kögl and Tonnies,⁷⁰ but its complex nature

68. Griffith, W. H.: The Nutritional Importance of Choline, *J. Nutrition* **32**: 239 (Sept.) 1941.

69. Griffith, W. H.: Personal communication to the author.

70. Kögl, F., and Tonnies, B.: Plant Growth Substances: XX. The Biotin Problem; Isolation of Crystalline Biotin from Egg Yolk, *Ztschr. f. physiol. Chem.* **242**: 43 (Aug.) 1936.

and, more important, its minute concentration in natural products has delayed complete identification of its structure even up to the date of this review. Its empirical formula $C_{10}H_{10}O_3N_2S$ has been found by du Vigneaud⁷¹ to consist of a cyclic derivative of urea which, on oxidation, yields adipic acid.

Both the free biotin and the methyl ester have been prepared and possess crystalline structures. Biotin is a very stable compound, resisting autoclaving with strong mineral acids, and in the form found in natural products is but slowly inactivated with strong alkali. The pure biotin, however, shows appreciable lability to alkali. Both free and bound biotin are inactivated by oxidizing agents.

It has been known for many years that a characteristic syndrome can be produced in rats fed diets containing rather high amounts of raw egg white. Lease, Parsons and Kelly⁷² found that the rabbit and the monkey also exhibited a characteristic dermatitis when fed rations rich in egg whites. As early as 1933 Parsons⁷³ concluded that the injury involved an interrelation between a positive toxicity and a relative absence of a protective factor, and a little later György named this factor vitamin H. Birch and György⁷⁴ obtained highly potent concentrates of the factor, and in 1940 du Vigneaud, Melville, György and Rose⁷⁵ first suggested the identity of biotin and vitamin H.

György, Rose, Eakin, Snell and Williams⁷⁶ have now established the presence of "avidin" (an albumin) as the biotin inactivating factor in egg white. Thus it becomes apparent that egg white injury is due to the unavailability of biotin by virtue of being tied up with avidin, in which complex biotin cannot be

71. du Vigneaud, Vincent; Hofmann, Klaus, and Melville, D. B.: On the Structure of Biotin, *J. Am. Chem. Soc.* **64**: 188 (Jan.) 1942.

72. Lease, Jane G.; Parsons, Helen T., and Kelly, Eunice: A Comparison in Five Types of Animals of the Effects of Dietary Egg White and of a Specific Factor Given Orally or Parenterally, *Biochem. J.* **31**: 433 (March) 1937.

73. Parsons, Helen T.; Lease, Jane G., and Kelly, Eunice: The Cure of Dermatitis Due to Egg White by Various Foodstuffs, *J. Biol. Chem.* **100**: lxxvii (May) 1933.

74. Birch, T. W., and György, Paul: Physiochemical Properties of the Factor (Vitamin H) Curative of Egg White Injury, *J. Biol. Chem.* **131**: 761 (Dec.) 1939.

75. du Vigneaud, Vincent; Melville, D. B.; György, Paul, and Rose, C. S.: On the Identity of Vitamin H with Biotin, *Science* **62**: 62 (July 19) 1940.

76. György, Paul; Rose, C. S.; Eakin, R. E.; Snell, E. E., and Williams, R. J.: Egg White Injury as the Result of Nonabsorption in Inactivation of Biotin, *Science* **63**: 477 (May 16) 1941.

absorbed from the intestine and is excreted in the feces. Nielsen and Elvehjem,⁷⁷ using a more complete ration than had been used in the early work, were able to demonstrate a biotin deficiency in the rat fed 10 per cent levels of egg white. Typical symptoms of "spectacled eye" progressing to general alopecia and, in the later stages, the onset of a spasticity and final death of the animal were recorded. Even the severe symptoms of spasticity were cured when excess biotin (in excess of that which unites with the avidin) was added to the diet. On the synthetic diet without the egg white these workers were unable to demonstrate any signs of biotin deficiency, and it seems probable that under most conditions the rat can synthesize, through the medium of bacteria in the intestine, sufficient biotin for its requirement. Biotin deficiency has been reported in the chick without resorting to egg white diets, which seems to indicate that very limited synthesis of biotin in the intestinal tract must prevail. A typical dermatitis involving the feet was found by Hegsted and his co-workers⁷⁸ to be characteristic of the deficiency in the chick; and Patrick and his co-workers⁷⁹ also have noted similar dermatitis with turkeys on biotin deficient rations.

Biotin can be conveniently determined by use of microbiologic methods of assay in which responses in yeast growth (Snell, Eakin and Williams⁸⁰) or acid production by *Lactobacillus casei* (Shull, Hutchings and Peterson⁸¹) are measured. Biotin is quite ubiquitous in distribution, but liver, kidney, yeast and egg yolk are the chief sources. It is to be emphasized that in most tissues biotin is present in a "bound" state in which it cannot be extracted by hot water, and autolysis or acid hydrolysis must be employed to realize the true concentration of biotin in these instances. As for the clinical applications of biotin, it is needless to point

77. Nielsen, E., and Elvehjem, C. A.: Cure of Spectacle Eye Condition in Rats with Biotin Concentrates, *Proc. Soc. Exper. Biol. & Med.* **48**: 349 (Oct.) 1941.

78. Hegsted, D. M.; Oleson, J. J.; Mills, R. C.; Elvehjem, C. A., and Hart, E. B.: Studies on a Dermatitis in Chicks Distinct from Pantothenic Acid Deficiency, *J. Nutrition* **20**: 599 (Dec.) 1940.

79. Patrick, H.; Boucher, R. V.; Dutcher, R. A., and Knandel, H. C.: Biotin and Prevention of Dermatitis in Turkey Poults, *Proc. Soc. Exper. Biol. & Med.* **48**: 456 (Nov.) 1941.

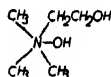
80. Snell, E. E.; Eakin, R. E., and Williams, R. J.: Quantitative Test for Biotin and Observation Regarding Its Occurrence and Properties, *J. Am. Chem. Soc.* **62**: 175 (Jan.) 1940.

81. Shull, G. M.; Hutchings, B. L., and Peterson, W. H.: A Microbiological Assay for Biotin, *J. Biol. Chem.* **143**: 913 (Feb.) 1942.

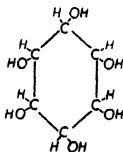
out the futility of even attempting human experimentation until a great deal more of the fundamental work has been accomplished. As soon as crystalline biotin becomes more generally available, this fundamental work will be forthcoming.

INOSITOL

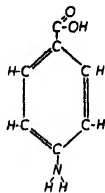
The position of inositol among the B vitamins is only tentative; but, since several workers have obtained responses with this compound, presentation of their work is warranted. Inositol is a crystalline substance with a sweet taste, the formula of which is isomeric with d-glucose. Its structure shows it to be a hexahydroxy cyclohexane.



Choline



Inositol



p-Aminobenzoic acid

It is an extremely stable compound resisting strong acid and alkali treatment. It is found in plants, where it occurs as "phytin," a calcium magnesium salt of inositol phosphoric acid. In the body, inositol is found in muscle (accounting for the term "muscle sugar"), brain, blood erythrocytes and eye tissues, but its function is still only a matter of speculation. The relation of inositol to the nutrition of animals was first indicated by the report of Woolley,⁸² who isolated the substance from liver and showed it to be the constituent factor responsible for the cure of mouse alopecia. Later Pavcek and Baum⁸³ were able to demonstrate a growth response and a cure of spectacled eye in rats. The curative action and growth effect of inositol seemed to be related to the amount and type of fat in the diet, since the syndrome was produced on fat free or low butter fat rations and not on those containing 14 per cent Crisco (unpublished data). Sure⁸⁴ has presented

82. Woolley, D. W.: The Nature of the Antialopecia Factor, *Science* 93: 384 (Oct. 25) 1940.

83. Pavcek, P. L., and Baum, H. M.: Inositol and Spectacled Eye in Rats, *Science* 93: 502 (May 23) 1941.

84. Sure, Barnett: Dietary Requirements for Fertility and Lactation: XXX. Role of p-Aminobenzoic Acid and Inositol in Lactation, *Science* 94: 167 (Aug. 15) 1941.

data which indicate that inositol may be required by the lactating rat. Martin, Thompson and de Carvajal Ferero⁸⁵ have injected rather low levels (10 mg. per kilogram of body weight) of inositol into dogs and found intestinal motility to be greatly increased. A definite growth increment in the chick was obtained on feeding inositol in conjunction with a synthetic ration.⁸⁶ In the rat, inositol was found to have an effect similar to lipocaic in preventing the fatty livers produced by the feeding of liver fractions or purified biotin preparations.⁸⁷

Inositol can be determined in tissues and foods by using a microbiologic assay employing a specific strain of yeast as the test organism.⁸⁸ By this method of determination, Williams and his co-workers⁸⁹ have run large numbers of assays on various rat and beef tissues and found spleen, heart, kidney, brain, thyroid and testes to be especially high in inositol. As previously mentioned, inositol in the form of phytin, is present in large amounts distributed throughout the plant kingdom; cereal brans and seeds are exceptionally good sources. No work has been done on the possible significance of inositol in human nutrition.

PARA-AMINOBENZOIC ACID

Another factor which was first recognized through its effect on bacterial growth⁹⁰ and which now shows indication of a vitamin-like action in animals is a rather simple derivative of benzoic acid—para-aminobenzoic acid.

Ansbacher⁹¹ has produced graying of the fur of rats on a synthetic ration which could be cured by the administration of 3 mg. of para-aminobenzoic acid daily. It should be mentioned that this achromotrichia was

85. Martin, G. J.; Thompson, M. R., and de Carvajal-Ferero, J.: Influence of Inositol and Other B Complex Factors on the Motility of the Gastrointestinal Tract, *Am. J. Digest.* **8**: 290 (Aug.) 1941.

86. Hegated, D. M.; Briggs, G. M., Jr.; Mills, R. C.; Elvehjem, C. A., and Hart, E. B.: Inositol in Chick Nutrition, *Proc. Soc. Exper. Biol. & Med.* **47**: 376 (Jan.) 1941.

87. Gavin, Gertrude, and McHenry, E. W.: Inositol: A Lipotropic Factor, *J. Biol. Chem.* **139**: 485 (May) 1941.

88. Woolley, D. W.: A Method for the Estimation of Inositol, *J. Biol. Chem.* **140**: 453 (Aug.) 1941.

89. Williams, R. J.; King, Anne; Mitchell, H. K., and McMahan, J. R.: Assay Method for Inositol. Studies on the Vitamin Content of Tissues: I, University of Texas Publication 4137, Oct. 1, 1941, p. 27.

90. Rubbo, S. D., and Gillespie, J. M.: Para-Aminobenzoic Acid as a Bacterial Growth Factor, *Nature* **146**: 838 (Dec. 28) 1940.

91. Ansbacher, Stefan: P-Aminobenzoic Acid, a Vitamin, *Science* **63**: 164 (Feb. 14) 1941.

not related to pantothenic acid, since the ration contained an adequate amount of this vitamin. A growth response in chicks maintained on a vitamin K deficient ration was also obtained when 300 micrograms of para-aminobenzoic acid per gram of ration was added. Sure,⁸¹ in experiments involving pregnancy and lactation in rats, has observed definite responses to para-aminobenzoic acid. There is some evidence in clinical experiments that restoration of hair pigment may occur,⁸² but more extensive experiments both in animal and in clinical trials are necessary before the vitamin nature of the substance can be clearly established.

OTHER FACTORS OF THE B COMPLEX

Although the nine crystalline factors that have been described include almost all of the B factors required by the rat, the use of the chick as the experimental animal gives evidence for the existence of several additional factors which, because of their water solubility, should be classed under the B vitamins. Schumacher, Heuser and Norris⁹³ have fractionated yeast and obtained two growth factors which could not be replaced in their activity by any of the known B vitamin combinations. The designation of R and S factors was applied to these fractions. The identity of one of these factors with the unknown eluate factor which Stokstad⁹⁴ postulates as being responsible together with pyridoxine for the activity of factor U is quite probable.

Aminoacetic acid, arginine and chondroitin were found through the experiments of Almquist⁹⁵ and Hegsted⁹⁶ as the factors responsible almost entirely for the growth responses due to cartilage and termed the "cartilage growth factor" by the Wisconsin workers. The amino acid cystine shows indications of stimulating

92. Sieve, B. F.: Clinical Achromotrichia, *Science* **94**: 257 (Sept. 12) 1941.

93. Schumacher, A. E.; Heuser, G. F., and Norris, L. C.: The Complex Nature of the Alcohol Precipitate Factor Required by the Chick, *J. Biol. Chem.* **135**: 313 (Aug.) 1940.

94. Stokstad, E. L. R.; Manning, P. D. V., and Rogers, R. E.: The Relation Between Factor U and Vitamin B₆, *J. Biol. Chem.* **132**: 463 (Jan.) 1940.

95. Almquist, H. J.; Stokstad, E. L. R.; Mecchi, E., and Manning, P. D. V.: Identification of the Rice Factor, *J. Biol. Chem.* **134**: 213 (June) 1940. Almquist, H. J.; Mecchi, E.; Stokstad, E. L. R., and Manning, P. D. V.: Identification of the Rice Factor: The Carbohydrate Component, *ibid.* **134**: 465 (June) 1940.

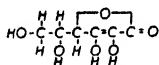
96. Hegsted, D. M.; Hier, S. W.; Elvehjem, C. A., and Hart, E. B.: Growth Factors in Cartilage for the Chick, *J. Biol. Chem.* **139**: 863 (June) 1941.

growth when fed to chicks on a synthetic ration, indicating the inadequacy of 18 per cent casein diets in this factor.⁹⁷ The factor required by *Lactobacillus casei* has been shown by Hutchings⁹⁸ to function in the nutrition of the chick, and it is highly probable from the comparison of chemical and other properties that it is identical with the "folic acid" of Williams and his co-workers⁹⁹ and what Stokstad¹⁰⁰ termed a "nucleotide."

The class of water soluble vitamins found in citrus fruits, vegetables and milk include ascorbic acid, vitamin P, the "grass juice factor" and the "milk factor."

ASCORBIC ACID, OR VITAMIN C

Ascorbic acid is a colorless crystalline compound with a mild acidic taste resembling that of citric acid and possesses the empirical formula $C_6H_8O_6$. The structural formula of l-ascorbic acid, the physiologically active isomer, is represented as follows:



l-Ascorbic acid

Ascorbic acid is easily destroyed in vegetables, as illustrated by loss of 50 per cent of the vitamin content of lettuce and spinach when stored at room temperature for several days. Cold storage is an effective means of preserving this factor in vegetables and fruits. Ascorbic acid is very easily oxidized, and its destruction during cooking is probably related to this fact. Neutral or alkaline solutions are more conducive to rapid destruction of ascorbic acid than are acid solutions.

Much evidence for the relation of ascorbic acid to specific enzyme systems is available from in vitro experiments, but whether these relationships function in the animal organism is not clear. An important

97. Briggs, S. M., Jr.; Mills, R. C.; Elvehjem, C. A., and Hart, E. B.: The Effect of Added Cystine in Purified Rations for Chicks, *J. Biol. Chem.* **144**: 47 (June) 1942.

98. Hutchings, B. L.; Bohonos, N.; Hegsted, D. M.; Elvehjem, C. A., and Peterson, W. H.: Relation of a Growth Factor Required by *Lactobacillus Casei* E to the Nutrition of the Chick, *J. Biol. Chem.* **140**: 681 (Aug.) 1941.

99. Mitchell, H. K.; Snell, E. E., and Williams, R. J.: The Concentration of "Folic Acid," *J. Am. Chem. Soc.* **63**: 2284 (Aug.) 1941.

100. Stokstad, E. L. R.: Isolation of a Nucleotide Essential for the Growth of *Lactobacillus Casei*, *J. Biol. Chem.* **139**: 475 (May) 1941.

argument against the theory of ascorbic acid functioning as a respiratory catalyst is the failure of deficient tissues to show decreases in respiration.

Deficiencies of ascorbic acid can be demonstrated only in man, the monkey and the guinea pig, the other species possessing the ability of synthesis of the vitamin. In infants, especially those artificially fed, periosteal hemorrhages occurring around the bones of the lower extremities are manifestations of the deficiency, while, in adults, petechial hemorrhages into the skin, bleeding into muscle tissue and bloody diarrhea are not uncommon signs. The relation of ascorbic acid to the restoration of the fertilizing capacity of the bull has been recently reported by Phillips and his co-workers.¹⁰¹ The ascorbic acid content of bull semen gives an index to the probable potency in breeding; low values or exceptionally high values of ascorbic acid are associated with an unreliable breeding record.

The vitamin can be easily determined by use of the dye 2-6 dichlorophenol indophenol, which is quantitatively reduced by ascorbic acid with the resulting formation of the colorless form of the dye and dehydroascorbic acid. Citrus fruits, spinach, berries, tomatoes and cabbage are excellent natural sources of ascorbic acid.

The recommended daily allowance for an average adult man is 75 mg., while the minimum requirement has been set at 30 mg. daily. The high requirement of the infant for this factor is provided for in the high concentration of ascorbic acid found in human milk as compared with cow's milk.

CITRIN (VITAMIN P)

A substance distinct from vitamin C has been reported as existing in paprika and lemon rind by Rusznyák and Szent-Györgyi.¹⁰² It has been termed "citrin" and found to consist of two flavonone components, hesperidin and demethylated hesperidin, or eriodictin. It has been difficult to demonstrate animal responses to such flavonones, but in several clinical trials definite indications of the functioning of these substances in certain hemorrhagic diseases is available. Szent-Györgyi

101. Phillips, P. H.; Lardy, H. A.; Heizer, E. E., and Rupel, I. W.: Sperm Stimulation in the Bull Through Subcutaneous Administration of Ascorbic Acid, *J. Dairy Sc.* **33**: 873 (Sept.) 1940.

102. Rusznyák, Stefan, and Szent-Györgyi, Albert: Vitamin P: Flavonols as Vitamins, *Nature* **135**: 27 (July 4) 1936.

and his co-workers¹⁰³ report improvement of capillary resistance and permeability in several cases of vascular purpura. Scarborough,¹⁰⁴ presenting data on 6 patients with generalized vitamin deficiencies, has evidence that intramuscular hemorrhages and gingival bleeding were alleviated by large doses of ascorbic acid, but capillary resistance remained low until vitamin P preparations made from orange juice or orange peel were administered. According to this author there exists a distinction between the spontaneous petechial hemorrhages of vitamin P deficiency and those associated with low intake of ascorbic acid.

Citrin, on reduction with magnesium in the presence of concentrated hydrochloric acid, forms a red color. Red is produced also when citrin is heated with sodium hydroxide. These reactions have been used by some workers for the estimation of this substance in fruits and vegetables, but poor agreement in the results points to the nonspecificity of the color tests.

GRASS JUICE FACTOR AND MILK FACTOR

On rations permitting good growth in the rat or those adequate for the chick, guinea pigs do not survive, indicating that other unknown factors are still lacking. The factor found in fresh grass which is required by the guinea pig has been called the "grass juice factor" by Kohler, Elvehjem and Hart.¹⁰⁵ Evidence for another factor, found in milk, concerned with stomach hemorrhages and ulcers in this animal is suggested by the work of Kohler, Randle, Elvehjem and Hart.¹⁰⁶ The usefulness of employing a variety of species of test animals in the elucidation of dietary essentials thus cannot be disputed.

From this short discussion it is obvious that the group of water soluble vitamins includes more than a dozen separate factors, many of which have found an important place in human nutrition. Additional factors have been added to this group within the past

103. Armentano, L.; Bentsath, A.; Beres, T.; Ruzsnyák, Stefan, and Szent-Györgyi, Albert: Ueber den Einfluss von Substanzen der Flavongruppe auf dem Permeabilität der Kapillaren: Vitamin P (The Influence of Flavonols on Capillary Permeability: Vitamin P) *Deutsche med. Wchnschr.* **63**: 1325 (Aug. 14) 1936.

104. Scarborough, Harold: Deficiency of Vitamin C and Vitamin P in Man, *Lancet* **2**: 644 (Nov. 23) 1940.

105. Kohler, G. O.; Elvehjem, C. A., and Hart, E. B.: Growth Stimulating Properties of Grass Juice, *Science* **83**: 445 (May 8) 1936.

106. Kohler, G. O.; Randle, S. B.; Elvehjem, C. A., and Hart, E. B.: Simplified Rations for Guinea Pigs Suitable for Assay of the Grass Juice Factor, *Proc. Soc. Exper. Biol. & Med.* **40**: 154 (Feb.) 1939.

two years, and some of these may have an equally important role when they are studied more extensively. I doubt that any one will deny the suggestion that there are several water soluble vitamins left to be identified.

The availability of the several synthetic water soluble vitamins has been of the greatest value in clinical practice, but the common foods still remain the best source of these vitamins in practical nutrition. Aside from the gustatory significance of properly prepared natural foods, the greatest value obtained from their consumption is that they supply the unknown factors along with

TABLE 2.—*Vitamin Content of Commercial Concentrates*

Sample No.	Milligrams per unit of product				
	Thiamine	Riboflavin	Nicotinic Acid	Pyridoxine	Pantothenic Acid
2.....	0.3	0.12	0.8	0.08
3.....	0.2	0.3	3.0	0.03	0.2
4.....	0.45	0.08	1.2
8.....	1.5	0.37	10.0	0.2	0.1
11.....	0.3	0.1
21.....	1.0	0.6	5.0	0.3	0.3
33.....	1.2	0.4	10.0	0.1	0.1
37.....	1.8	0.1	10.0	0.02
39.....	1.0	1.0	0.15	0.03	0.2
48.....	1.0	1.2	12.0	1.2	1.2
67.....	1.0	1.0	10.0	0.1	0.1
76.....	1.5	0.5	25.0	0.12	0.5
90.....	5.0	2.0	20.0	0.2
102.....	1.5	1.0	20.0	0.2	1.0
110.....	0.15	0.005	0.005	0.003

the known. All the known water soluble vitamins may be obtained from natural foods through proper selection. This selection is not an easy task even with the modern methods of food production and distribution. Some of the modern methods of processing increase rather than decrease the difficulties. Often more emphasis is placed on the mere use of natural foods than on the proper combination of these foods. The few values given in table 1 clearly indicate the fallacy of this emphasis. Different natural foods differ greatly in the amount of any given vitamin which they contain. Thus apples contain 0.02 mg. and pork loin 1.5 mg. of thiamine per hundred grams and both are natural foods. Eggs supply 0.05 mg. and peanuts 13 mg. of nicotinic acid per hundred grams. In addition, any one food

may show enormous variations in the amount of the different B vitamins present. Thus oatmeal contains 0.8 mg. of thiamine but only 0.1 mg. of riboflavin per hundred grams, while calf's liver contains 0.4 mg. of thiamine and 3.2 mg. of riboflavin per hundred grams. We still need to use a little ingenuity in compounding a complete diet even from natural foods.

There has been an increasing interest in eliminating the effect of this variation by prescribing vitamin concentrates. In other words, a tablet or a capsule may supply the daily requirement of the vitamins, and any pleasing combination of foods may be consumed for the rest of the day. A survey of the concentrates now on the market shows that this is a dangerous practice and that the composition of the concentrates varies just as much as natural foods. At my request Mrs. Sarah Ellen Wenger has studied the composition of one hundred and nineteen vitamin products manufactured by thirty-two different companies. The B vitamin content of a few of the products is given in table 2. The thiamine content varies from 0.15 to 5.0 mg., the riboflavin from 0.005 to 2.0 mg., the nicotinic acid from 0.005 to 25 mg., and so on. In a single product (No. 37) the thiamine is 1.8, the riboflavin 0.1, nicotinic acid 10.0, and vitamin B₆ 0.02 mg. These products may be useful in the treatment of specific deficiencies, but in practical nutrition they give us no greater security than the proper combination of natural foods. Thus we not only need to identify all the essential vitamins but we must give consideration to the distribution of these factors in foods and food preparations as well as the daily human requirements.

CHAPTER XII

FOODS OF PLANT ORIGIN

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Over 50 per cent of the American diet consists of foods of plant origin. Indirectly as foods for animals, plant products make an additional contribution to the human diet through their influence on the nutritive value of animal products.

In discussing nutritive values, it is necessary to make use of certain average figures for nutrient composition. Foods of plant origin are subject to rather wide variations in composition as influenced by genetic, soil and climatic factors. It is beyond the scope of this article to consider these factors. Their importance is illustrated by the study of Schultz and his co-workers¹ revealing wide variations in the thiamine content of wheat and of cereal grains of different origin. Some of the factors influencing mineral nutrition have recently been reviewed by Maynard² and by Beeson.³ Fortunately the consumer seldom gets his supply of a given food from a single agricultural source, and thus the significance of the wide variation in the composition of crops differently produced is not nearly so great as the individual values might suggest. There are also variations in foods as consumed caused by processing, storage and cooking factors. In the present article attention is called to these factors if they have a particular bearing on the significance of the average values cited. For convenience of discussion, the foods of plant origin are grouped as follows: cereals, legumes and nuts, potatoes, other root crops, tomatoes, leafy vegetables, miscellaneous vegetables, fruits, sugar, syrups and molasses and vegetable oils.

1. Schultz, A. S.; Atkin, L., and Frey, C. N.: A Preliminary Survey of the Vitamin B Content of American Cereals, *Cereal Chem.* **18**: 106 (Jan.) 1941.

2. Maynard, L. A.: Relation of Soil and Plant Deficiencies and of Toxic Constituents in Soils to Animal Nutrition, *Ann. Rev. Biochem.* **10**: 449, 1941.

3. Beeson, K. C.: The Mineral Composition of Crops with Particular Reference to the Soils in Which They Are Grown, *Miscellaneous Bulletin* 369, United States Department of Agriculture, March 1941.

CEREALS

Under cereals are included the cereal grains and their products, including flour, bread, breakfast foods, crackers, cookies, pastry and macaroni. Because of the low cost of cereals in relation to most other foods, their consumption is largest among the low income groups. The importance of these foods in the diet has been set forth editorially in *THE JOURNAL*⁴ as follows:

The cereal grains are the backbone of the nutrition of most of the races of the earth. They are, as a rule, the cheapest sources of food fuel; so that corn, wheat, rice, rye, barley and oat kernels are to be found constituting a third or often much more of the calory intake of the millions of persons involved.

Cereals also provide a third or more of the protein of the American diet. While this protein is not so high in biologic value as that of animal products, combina-

TABLE 1.—*Proximate Composition of Whole Wheat and of White Flour*

	Protein, per Cent	Fat, per Cent	Carbo- hydrates, per Cent	Crude Fiber, per Cent	Fuel Value per 100 Gm., Calories
Wheat flour, graham	13.0	2.0	72.4	1.8	360
Wheat flour, patent ...	10.8	0.9	75.9	0.3	340

tions of cereal and animal protein provide a diet of excellent protein quality. Important amounts of phosphorus, iron, copper and other minerals and of certain vitamins are supplied by cereals. Generalizations here are of limited value, however, because of the differences among cereals and the losses which result on milling.

Wheat.—Wheat is by far the leading cereal in the diet in the United States, furnishing approximately 25 per cent of the total calories consumed. The total per capita flour consumption for 1941 is estimated at 155 pounds (70 Kg.), 97 per cent of which was the milled product, leaving less than 5 pounds (2 Kg.) as whole wheat or graham flour. The consumption of wheat breakfast foods approximated 1½ pounds (0.7 Kg.) per capita. The proximate composition of the flours, as listed by Chatfield and Adams,⁵ is presented in table 1.

4. The Cereals in Nutrition, editorial, *J. A. M. A.* 95: 1101 (Oct. 11) 1930.

5. Chatfield, C., and Adams: Proximate Composition of American Food Materials, Circular 549, United States Department of Agriculture, June 1940.

It is clear that wheat makes a substantial contribution to the protein needs of the diet. Using the percentage figure for patent flour, one may calculate that the average daily consumption of $6\frac{8}{10}$ ounces (225 Gm.) of flour supplies 22 Gm. of protein daily, or nearly one-third the daily allowance. Whole wheat contains more protein than white flour, and its protein has a higher biologic value, but when white flour is supplemented with milk, eggs or meat, a protein mixture of high biologic value results. The much lower fiber content of patent flour reflects the removal of the bran in milling. While bran contributes laxative qualities to the diet, it is poorly digested and may be somewhat irritating to the mucous membranes of the digestive tract. The

TABLE 2.—*Vitamin and Mineral Content of Flours*

	Whole Wheat Flour, Mg./Lb.	White Flour, Mg./Lb.	Enriched Flour, Mg./Lb.
Thiamine.....	2.20	0.55	1.66
Riboflavin.....	0.50	0.15	1.20*
Nicotinic acid....	26.76	4.54	6.00
Iron.....	18.00	3.00	6.00
Pantothenic acid.....	6.03	2.59	
Pyridoxine..	2.09	0.99	

* Requirement suspended at present.

physiologic effects of bran have been reviewed by the Council on Foods.⁶

In table 2 are presented the vitamin and mineral values of whole wheat and white flour and, for comparative purposes, the minimum values set by the United States government for enriched flour. The values for thiamine, riboflavin, nicotinic acid and iron are taken from Ferrari.⁷ Those for pantothenic acid and pyridoxine were supplied by Elvehjem.⁸

The large milling losses of vitamins and minerals are evident from this table. The data show that the outstanding superiority of enriched flour over ordinary white flour lies in its fivefold increase in thiamine content, the figure being 75 per cent of that for whole wheat

6. Council on Foods: The Nutritional Significance of Bran, J. A. M. A. **107**: 874 (Sept. 12) 1936.

7. Ferrari, C. G.: Vitamin and Mineral Enrichment of Foods, Northwestern Miller **210**: 3 (April 29) 1942.

8. Teply, L. J.; Strong, F. M., and Elvehjem, C. A.: Nicotinic Acid, Pantothenic Acid and Pyridoxine in Wheat and Wheat Products, J. Nutr. **24**: 167-174, 1942.

flour. On the other hand, the enrichment in nicotinic acid and iron is small compared with the amounts present in whole wheat flour. The data show that milling results in a 60 per cent loss of pantothenic acid and a 50 per cent loss of pyridoxine. Much of the phosphorus and certain other minerals is also lost.

The enriched flour now on the market is nearly all produced by adding the nutrients in question to the refined product. A somewhat similar result can be achieved by "longer extraction" in milling, that is by retaining some of the vitamin and mineral rich portions of the wheat which are milled out in making patent flour. This is the procedure officially adopted in Canada, as described by Tisdall and his associates⁹ and by Newman.¹⁰

Wheat flour is consumed to a large extent in the form of bread, of which 85 per cent is commercially baked. Most of this bread is made from white flour, but it is estimated that approximately 60 per cent of the bread now consumed is the enriched product. This enriched bread is obtained either by the use of enriched flour or enriched yeast or by the direct addition of the specified minerals and vitamins to the dough.

An important factor in the nutritive value of bread is the extent to which skim milk solids are used in its manufacture. Six per cent of these is mentioned as the desirable amount in modern bread, but apparently much bread is made with 3 per cent or even less when the cost of skim milk is high. Whole wheat bread is commonly made without milk solids. The inclusion of 6 per cent of the solids increases the calcium content of white bread four times and the phosphorus content twice and adds 60 micrograms of thiamine and 360 micrograms of riboflavin per pound. It also improves the protein value considerably.

The proposed minimum standards which are now being followed for enriched bread are, per pound, thiamine 1 mg., riboflavin 0.8 mg., nicotinic acid 4 mg. and iron 4 mg.⁷ A similar content of skim milk solids being assumed, the thiamine content is approximately three times as large as that of ordinary bread, the iron

9. Tisdall, F. F.; Jackson, S. H.; Drake, T. G. H.; Newman, L. H.; Whiteside, A. G. O.; Miller, H., and Edgar, J.: The Retention of the Wheat Vitamins in Flour and Bread, a Problem of National Importance, *Canad. M. A. J.* 45: 101 (Aug.) 1941.

10. Newman, L. H.: The Retention of B Vitamins in Flour and Bread, *J. Am. Soc. Agronomy* 34: 109 (Feb.) 1942.

content is doubled and the nicotinic acid content is increased slightly. In these and in other nutrients the enriched product falls considerably short of whole wheat bread.

Since whole wheat bread contains the bran which is largely absent in white or in enriched bread, the question of relative digestibility is an important one. This question was thoroughly studied by Rubner¹¹ during World War I. He found that the advantage of the higher protein content of the unmilled product was offset by its lower digestibility and that it contained slightly less total available calories. Noteworthy modern studies have recently been published by Murlin and his associates.¹² The first study shows that whole wheat bread has in general a lower protein digestibility value but a higher protein biologic value. The second study reveals no significant differences in the digestibility of the carbohydrates of the two breads. The authors point out that any differences in protein or in available energy values are small and of little importance as compared with differences in vitamins and minerals.

Corn.—Corn meal is the chief form in which corn is used as human food, representing a per capita consumption of $23\frac{4}{10}$ pounds (11 Kg.) in 1939. An additional 8 pounds (4 Kg.) is consumed as breakfast foods, grits, hominy and canned corn.

The corn grain is approximately equal to the wheat grain in thiamine content but contains only one-fourth as much nicotinic acid. It is a good source of phosphorus and iron and certain other minerals. But much of the corn meal and flour consumed, as well as the hominy, grits and breakfast foods, is in the form of milled products. The milling process removes the germ and the bran and thus takes out most of the thiamine and minerals present in the entire kernel. The corn products must therefore be considered to be primarily energy yielding foods. They contain 8 to 9 per cent of protein, which ranks below wheat in biologic value but which combines with milk to provide a protein mixture

11. Rubner, M.: Die Verdaulichkeit von Weizenbrot, Arch. f. Anat. u. Physiol., 1916, p. 61.

12. Murlin, J. R.; Marshall, Margaret E., and Kochakian, C. D.: Digestibility and Biological Value of Whole Wheat Breads as Compared with White Bread, J. Nutrition 22: 573 (Dec.) 1941. Sealock, R. R.; Basinski, D. H., and Murlin, J. R.: Apparent Digestibility of Carbohydrates, Fats and "Indigestible Residue" in Whole Wheat and White Breads, ibid. 22: 589 (Dec.) 1941.

of high quality. Yellow corn meal differs from the white variety, as well as from other cereals, in containing a significant amount of vitamin A: 350 to 500 international units per hundred grams. In view of the rather large consumption of corn meal and other milled corn products by certain groups of the population, the wider use of the unmilled meal or the development of milling methods which would retain nutrients now lost would be highly desirable.

Canned corn is equal to corn meal in energy and protein on an equivalent moisture basis and is superior to the milled product in mineral and thiamine content.

Oats.—Among the breakfast food cereals, oatmeal and rolled oats, the principal forms in which oats are consumed, rank first both in quantity eaten and in nutritive value. Approximately 529 million pounds (240 million Kg.) is consumed annually. In the milling of oats, only the fibrous hull and the adhering portions are removed, the germ and the other vitamin-rich and mineral-rich portions being left with the product used for human food. Thus oatmeal ranks nutritionally as a whole grain cereal rather than as a milled product.

Oat cereals rank above wheat products both in fuel value and in protein content. Their higher fuel value is due primarily to their fat content (7.4 per cent). Their protein content, of over 14 per cent, outranks that of white wheat flour in biologic value. Both oatmeal and rolled oats are low in crude fiber and when properly cooked are highly digestible.

Oatmeal is considerably richer than whole wheat in thiamine. Aughey and Daniel¹³ reported that one hundred and twenty minutes' cooking in a double boiler did not cause any appreciable loss of thiamine from rolled oats. According to Andrews, Boyd and Terry,¹⁴ the riboflavin content of the oat grain averages 0.58 mg. per pound. Elvehjem^{14a} has found the following values for other vitamins in oats: nicotinic acid 4.5 to 6.8 mg. per pound, pantothenic acid 12.2 to 13.6 mg. per pound and pyridoxine 0.72 to 0.90 mg. per pound. It seems probable that most of the vitamin content here represented remains in the cereal after milling.

13. Aughey, Elizabeth, and Daniel, Esther P.: Effect of Cooking on the Thiamine Content of Foods, *J. Nutrition* **19**: 285 (March) 1940.

14. Andrews, J. S.; Boyd, H. M., and Terry, D. E.: The Riboflavin Content of Cereal Grains and Bread and Its Distribution in Products of Wheat Milling, *Cereal Chem.* **19**: 55 (Jan.) 1942.

14a. Elvehjem, C. A.: Personal communication to author.

Oatmeal is a rich source of iron (5.2 mg. per hundred grams) and copper (7.38 parts per million). Its phosphorus content, 66 per cent of which is in the form of phytin, is similar to that of whole wheat.

Rice.—Rice supplies slightly more than 1 per cent of the calories of the average American diet, the annual per capita consumption being approximately 5 pounds (2 Kg.). White, or milled, rice, the form in which most of the consumption occurs, is essentially an energy food. The protein content is around 7.5 per cent, thus being lower than that of corn. Over 50 per cent of the minerals and 85 per cent of the thiamine of the entire kernel are lost in milling. In contrast, brown rice, the product that results when only the hull is removed, contains 0.7 to 0.9 mg. of thiamine per hundred grams. It is nutritionally superior in other respects also. A change from white to brown rice would certainly be in the interests of better nutrition.

Rye.—The consumption of rye, mostly as milled rye flour in bread, is less than 3 pounds (1.3 Kg.) per capita annually. This flour is similar to white wheat flour in energy and in protein content. The whole grain contains approximately 2.4 micrograms of thiamine per gram.^{14b} Although some of the vitamins are lost when rye flour is degerminated and bleached it is still a better source of most of the B-complex factors than white wheat flour.

Barley.—A small amount of barley is consumed as pearl barley and as barley flour for infant feeding. These are milled products which are apparently similar to white wheat flour in energy value but lower in protein content. Milling has removed minerals and vitamins to an extent similar to that in which it removes them from wheat.

LEGUMES AND NUTS

Dry legume seeds, such as beans, peas and lentils, are approximately twice as rich in protein as the cereals. While most legume proteins are of rather low biologic value when fed alone, their deficiencies are made up by other proteins in a mixed diet. Dried beans, either home cooked or canned, are noteworthy as a cheap

14b. Ihde, A. J., and Schuette, H. A.: Thiamine, Nicotinic Acid, Riboflavin and Pantothenic Acid in Rye and Its Milled Products, J. Nutr. 22: 527-533, 1941.

source of protein even though the digestibility is somewhat less than for protein from many other sources.

Dried navy and kidney beans, green or dried lima beans, green or dried peas, lentils and cow peas are all rich sources of thiamine, containing around 0.5 mg. per hundred grams of the dried seed. A part of this thiamine is lost, however, in the cooking process. Two-thirds cup of baked, canned beans should nevertheless supply one eighth of the day's thiamine requirement. These legumes also supply significant amounts of riboflavin. Fresh green lima beans and peas are rich in ascorbic acid, but a large loss is involved in cooking. The legume seeds are noteworthy also for their iron content, the dried products containing from 6 to 10 mg. per hundred grams. Two-thirds cup of baked beans will supply one-fourth the daily adult allowance. Legume seeds are notably higher in calcium and in phosphorus than are even the whole cereal seeds.

It is evident that a larger consumption of dried legumes, particularly in place of refined cereals, would improve the diet in several respects. Their cheapness commends them especially for use in low cost diets.

Green and yellow string and wax beans, classed as seed pods, are comparable to the legume seeds in protein, minerals and thiamine per unit of dry matter and in addition contain notable amounts of vitamin A, riboflavin and ascorbic acid.

Peanuts have nutritive values similar to those of the other legumes, but in addition contain vitamin A, have a much higher energy value and the protein is of high biologic value. Peanut butter has a nutritive value similar to that of peanuts. Soybeans are nutritionally similar to peanuts. They are little used as human food in this country. Walnuts are comparable to peanuts in thiamine content, but almonds and pecans have somewhat less. All three have a high fat and a high protein content and are comparable to peanuts as sources of calcium and phosphorus.

VEGETABLES

Under the heading "Vegetables" are grouped a great variety of foods which differ widely in their nutritive values.

Potatoes.—According to United States Department of Agriculture statistics, 305,200,000 bushels of white

or Irish potatoes were consumed in the United States in 1939, or approximately 138 pounds (63 Kg.) per capita. Thus potatoes provide approximately 4 per cent of the total calory needs on the average. For many people, however, particularly the lower income groups, potatoes make up a much larger part of the diet than this average figure indicates, and their nutritive value is of added concern accordingly.

Potatoes are primarily an energy food, consisting largely of starch. Approximately 10 per cent of the total calories are in the form of protein of good biologic value. The potato is low in fiber, and according to various investigators it is highly digestible (92 to 99 per cent being used). It is a significant source of iron, in that one medium-sized potato may provide as much as one-tenth of the daily requirement.

As harvested, potatoes contain 12 to 35 mg. of ascorbic acid per hundred grams and thus provide a substantial amount of this vitamin. There is a continuous loss in storage, however, which amounts to 50 to 70 per cent in twelve months. The initial loss is rapid. There is a further loss in cooking, ranging from 14 to 66 per cent according to the procedure, as reported by Esselen and coworkers.¹⁵

The thiamine content of the potato ranges from 95 to 165 micrograms per hundred grams, which would mean from 8 to 14 per cent of the adult daily requirement in a 150 Gm. serving (approximately the average daily consumption) if it were not for cooking losses. The potato does not supply a significant amount of riboflavin. Iron is richest in the outer portions of the potato; vitamin C seems to be evenly distributed throughout. There is evidence that the vitamin and mineral loss is less in potatoes boiled with the skins on than when baked, but the loss is greatest for peeled potatoes.

The consumption of sweet potatoes in pounds is only about 25 per cent that of the white variety previously discussed, but it is approximately 35 per cent in terms of calories, owing to the higher dry matter content of the sweet variety. Like the white, the sweet potato is primarily an energy food, low in fiber and highly digesti-

15. Esselen, W. B.; Lyons, M. E., and Fellers, C. A.: *The Composition and Nutritive Value of Potatoes with Special Emphasis on Vitamin C*, Mass. Agr. Exper. Sta. Bull. 390, March 1942.

ble. Only 6 per cent of the total calories are in the form of protein, as compared with 10 per cent for the white variety.

Sweet potatoes are especially noteworthy, however, for their vitamin A value. Booher¹⁶ gives a value of 3,460 international units per hundred grams of the cooked product. Thus an average sized serving would supply two-thirds the adult daily allowance of 5,000 international units.¹⁷ Sweet potatoes are apparently similar to white in vitamin C content but lower in thiamine. They are also lower in iron and make no significant contribution to the diet as regards other minerals, except possibly in certain trace elements. An excellent study of the nutritive value of dehydrated sweet potatoes has recently been published by Lease and Mitchell.¹⁸

Other Root Crops.—Among other root crops the carrot is high in carotene content. Converting the carotene into international units of vitamin A the values range from 2,200 to 10,000 units per hundred grams, so that approximately three-fourths of a cup of cooked carrots should furnish one-third to three-fourths of the daily adult allowance. However, there is some question as to how well carotene from various sources is utilized by the body. According to experiments at the U. S. Plant, Soil and Nutrition Laboratory at Cornell University the white rat utilized only 33 per cent of the carotene from carrots. Utilization values as low as 1 to 19 per cent for man have been reported in the literature.

Compared with the carrot on a calory basis, turnips furnish similar amounts of thiamine, riboflavin, iron and protein, 50 per cent more calcium and eight times as much vitamin C. Swede juice has been reported one-

16. Booher, Lela E., and Marsh, R. L.: The Vitamin A Values of 128 Foods as Determined by the Rat Growth Method, Tech. Bull. 802, United States Department of Agriculture, December 1941.

17. In setting up this allowance, it was recognized that somewhat more would be required if all the units were furnished as carotene and somewhat less if all were furnished by vitamin A itself, because a unit in the form of carotene may be, under certain conditions at least, only about half as effective in human nutrition as a unit of vitamin A itself. Thus, the rating here given for sweet potatoes, while accurate for comparison with other plant sources of vitamin A, overrates the vegetable in comparison with a source of vitamin A itself. The same considerations apply to later discussions of the vitamin A value of the foods included in this paper.

18. Lease, E. J., and Mitchell, J. H.: Biochemical and Nutritional Studies of Dehydrated Sweet Potato, Bull. 329, South Carolina Agricultural Experiment Station, June 1940.

half as rich as orange juice. One-half cup of properly cooked turnips should supply approximately one-fifth the adult daily allowance of ascorbic acid. Beets are similar to carrots as regards riboflavin and vitamin C content and contain more iron and protein. Raw onions are also a good source of vitamin C according to Murphy,¹⁹ but storage losses range from 14 to 50 per cent, and thus old onions are not a reliable source.

Tomatoes.—Tomatoes are one of the most important protective foods, both because of their special nutritive values and because of their widespread production. They rank third in quantity among the vegetable crops, being exceeded only by white and sweet potatoes. Among the canned vegetables, the tomato in its various forms ranks first.

Tomatoes are outstanding as a source of ascorbic acid, having an average content of 25 mg. per hundred grams for the summer grown products. Thus one small tomato will supply about one-third the recommended daily allowance for the adult (75 mg.). The acidity of the tomato protects it against any considerable loss in cooking unless soda is used in the process. In the canning of tomatoes and tomato juice there is little loss of the vitamin if the process is properly carried out. One 5 ounce (150 cc.) glass of tomato juice supplies about one-third the daily allowance. Recent evidence indicates that tomatoes as purchased on the northern markets in winter contain much less ascorbic acid than those available in summer.

Tomatoes are also rich in carotene. Ripe tomatoes, fresh or canned, contain approximately 1,000 international units of vitamin A per hundred grams. This means that one small tomato or a 5 ounce glass of canned juice will supply about one-fifth the daily adult allowance.

On the basis of the available figures, tomatoes in the amounts consumed cannot be considered as an important source of any of the B group of vitamins or of the mineral elements with the possible exception of iron.

Leafy Vegetables.—The leafy vegetables, including cabbage, kale, chard, broccoli, spinach, turnip greens, collards, lettuce and beet greens, are outstanding sources of certain minerals and vitamins. They are particu-

19. Murphy, E. F.: Ascorbic Acid Content of Onions and Observations on Its Distribution, Food Research 6: 581 (Nov.-Dec.) 1941.

larly noteworthy for their calcium, the important element in which cereals, potatoes and most other foods except milk and cheese are deficient. Among the leafy vegetables mentioned, turnip greens rank at the top in calcium content. One-half cup (3 ounces, or 90 cc.) of the cooked greens will supply approximately one-third the daily adult allowance. Broccoli, collards, kale, loose leaf lettuce and mustard greens are also rich sources. Head lettuce and cabbage are relatively low, but cabbage greens and the outer leaves of cabbage rank even higher than turnip greens.

Experiments by Fincke²⁰ have shown that the calcium content of broccoli and that of cauliflower are nearly as available as that of milk. Speirs²¹ has reported that the utilization of calcium from turnip greens is about equal to that from milk but that the calcium in tender greens, collards and kale is less well utilized. The calcium of spinach, beet greens, chard and lamb's-quarters is not nutritionally available because of the high oxalic content of these vegetables.

The calcium contribution of green leafy vegetables becomes particularly important in diets containing little milk or cheese.

The green leafy vegetables are important sources of iron. A serving (3 ounces) of cooked turnip greens, mustard greens, spinach, chard or beet greens will supply approximately 25 per cent of the adult daily allowance. Kale supplies somewhat less, and headed lettuce and cabbage are relatively poor sources.

The green leafy vegetables are all rich sources of carotene and thus make an important contribution to the vitamin A content of the diet. Sherman²² gave a range of 13,000 to 27,000 international units per hundred grams for kale, chard, spinach, turnip greens, dandelion greens and mustard greens. The greener and leafier the product, the higher is the vitamin A content. Carotene from green leafy vegetables seems to be better utilized than that from the yellow vegetables. Allowing for losses in cooking and for the fact that the vitamin allowance must be higher when carotene is the

20. Fincke, M. L.: The Utilization of the Calcium of Cauliflower and Broccoli, *J. Nutrition* **22**: 477 (Nov.) 1941.

21. Speirs, Mary: The Utilization of Calcium in Various Greens, *J. Nutrition* **17**: 557 (June) 1939.

22. Sherman, H. C.: *Chemistry of Foods and Nutrition*, ed. 2, New York, Macmillan Company, 1941.

source, a 3 ounce serving of one of these greens can be relied on to meet more than the day's needs. Headed cabbage and lettuce are relatively poor sources.

In the fresh state, the leafy vegetables are excellent sources of vitamin C. A cup of raw shredded cabbage will furnish nearly a third of the day's allowance. Watercress, collards, broccoli, turnip greens, mustard greens and kale are similar in vitamin C content to cabbage; beet greens and dandelion greens contain somewhat less; lettuce, escarole and endive contain much less. Leafy vegetables lose vitamin C by oxidation in storage and also in cooking. Further losses occur by solution in cooking if the cooking water is discarded. Gould, Tressler and King²³ found that, in cooking, 25 per cent of the vitamin C of cabbage was destroyed by oxidation and another 25 per cent lost in the cooking water. Other vegetables have shown similar losses. In the preparation of vegetables, further destruction of vitamin C by oxidation occurs when they are crushed or bruised or allowed to stand for long periods of time at room temperature both before and after cooking. Cutting and chopping into small pieces also accelerates the oxidation of vitamin C but in order to reduce the cooking time it is sometimes advisable to do this with large vegetables, particularly if they are cooked in very small amounts of water. Vitamin C losses can be decreased by refrigerating the vegetable until ready to prepare and serve. In cooking use as little water as possible, have the water boiling to start with, bring the water back to the boil quickly after adding the vegetables and keep the cooking time at a minimum. The same methods which help to conserve the vitamin C value will also conserve riboflavin, thiamine and mineral values. All these food components are more or less water soluble.

Most of the green leafy vegetables are excellent sources of riboflavin, the leaves being much richer than the stems. A serving of cooked beet greens will supply about one-fourth of the daily adult allowance. Spinach and kale supply about one-fifth. Other greens supply a lesser amount, headed cabbage and lettuce ranking at the bottom of the list. Leafy vegetables are not a

23. Gould, Stella; Tressler, D. K., and King, C. G.: Vitamin C Content of Vegetables: V. Cabbage, *Food Research* 1: 427 (Sept.-Oct.) 1936.

good source of thiamine, furnishing only 3 to 9 per cent of the adult daily allowance. The destruction in cooking usually does not exceed 10 to 15 per cent, but the addition of soda increases destruction, and when large amounts of water are used and discarded, large additional losses occur by solution. Certain leafy vegetables have been found effective in preventing and curing pellagra, but there are practically no data available regarding their specific nicotinic acid content.

In the amounts commonly consumed, leafy vegetables are of little significance as energy foods, but their higher carbohydrate content provides roughage, which is needed in certain diets. They are relatively richer in protein than in calories, and their protein ranks above seed proteins in general in biologic value. However, the actual contribution to the diet in the amounts commonly consumed is small.

Miscellaneous Vegetables.—There are several other vegetables which, although limited as to general use, make important contributions to the diet of certain groups. The Hubbard, or winter, variety of yellow squash contains 6,000 international units of vitamin A per hundred grams. One-half cup of the cooked product supplies nearly one-half the adult daily allowance. Summer squash contains much less. Pumpkin furnishes approximately one-fourth as much as winter squash.

A serving of fresh asparagus (nonbleached) can furnish approximately one-seventh the day's allowance of vitamin A and one-sixth that of vitamin C. It is also a significant source of calcium and iron. Brussels sprouts are rich sources of vitamin C and also furnish significant amounts of iron, calcium and vitamin A. Cauliflower is notable for its content of ascorbic acid, thiamine and riboflavin.

One medium sized sweet pepper will furnish 870 international units of vitamin A and 180 to 200 mg. of vitamin C. Chili peppers, whether fresh or dried, are a good source of vitamin A. Fresh chili is an excellent source of vitamin C. Some of the vitamin C is retained on canning. Okra contains 2,200 international units of vitamin A per hundred grams. Parsley, which is used mainly for decoration, is an excellent source of both vitamin A and iron. When fresh it furnishes some vitamin C.

FRUITS

According to United States Department of Agriculture statistics for 1939, the present per capita consumption of fruits, calculated on the fresh basis, was 221 pounds (100 Kg.). Of this total, 75 per cent was consumed fresh and 15 per cent canned, and the remainder was divided between dried fruits and juices. Apples outranked all other fruits, representing over one-fourth the total consumption. But citrus fruits as a class exceeded apples by 50 per cent or more. The nutritive values of various fruits have been excellently summarized in a recent article by Morgan,²⁴ and I have drawn on this article for many of the data which follow.

Fruits do not contribute important amounts of either calories or proteins to the diet, but they are of outstanding value because of their content of certain vitamins and minerals. As a class, fruits are important sources of ascorbic acid, certain members of the B complex, vitamin A, iron and other minerals, but there is a large variation among the different kinds as regards the extent of their contributions.

The citrus fruits are especially important for their ascorbic acid content. A medium-sized orange weighing around 5½ ounces (155 Gm.) will meet the daily adult allowance. A somewhat greater weight of grapefruit is required. Four and one-half ounces (130 Gm.) of canned orange or lemon juice or 6 ounces (170 Gm.) of canned grapefruit juice would supply the daily allowance. While the citrus fruits cannot be considered important sources of other nutrients, they do contain iron, calcium and thiamine in amounts which are of some significance in the diet. Pineapples, which are consumed mostly canned or as juice, contain about half as much vitamin C as do citrus fruits and are in general similar in other values.

Apricots and yellow peaches are important sources of vitamin A. The day's adult allowance is supplied by 3½ ounces (100 Gm.) of fresh or canned apricots or by approximately three times as much fresh or canned peaches. Weight for weight, dried peaches and dried apricots supply approximately three times as much vitamin A as the fresh products. Canteloupes contain about half as much of this vitamin as do fresh peaches.

24. Morgan, A. F.: *A Nutritive Index of Fruits, Fruit Products J.* 21:75 (Nov.) 1941.

and they are an important source of ascorbic acid. Dried prunes furnish significant amounts of vitamin A, riboflavin and thiamine. Plums rank above other fresh fruits in thiamine content. Apricots, peaches and to a lesser extent prunes are significant sources of iron.

Apples cannot be considered a large source of any vitamin or mineral nutrient. In view of their large consumption, however, they do make a significant contribution of ascorbic acid to the diet. A medium sized apple weighing 6 ounces supplies on the average about one-tenth the day's allowance, but there are decided differences among varieties. The keeping qualities of apples make it possible for them to be marketed throughout the winter in latitudes where fresh grown sources of vitamins are unavailable or high in price. In rural areas in which they are produced, home stored apples undoubtedly make an important contribution of ascorbic acid to the diet during the winter season, when the problem of getting adequate supplies of this vitamin is most difficult. Apples also contain a significant amount of iron. There is a 25 per cent loss of vitamin C in making applesauce. The loss is greater when apples are baked or made into pie.

Bananas are similar to apples in vitamin C value: they contain almost twice the iron. Bananas are a significant source of vitamin A.

Fresh strawberries are another food high in vitamin C, the range for eleven varieties being between 40 to 104 mg. per hundred grams. Thus one-half cup would supply from two-thirds to more than the daily need for ascorbic acid.²⁵

SUGAR, SYRUPS AND MOLASSES

White sugar contributes only calories to the diet. It is clear that the present large consumption of sugar is disadvantageous in that it means a smaller consumption of nutritionally superior foods. Furthermore, there is evidence that sugar is a factor in tooth decay. Brown sugar, corn syrup, honey, maple syrup and maple sugar contain small amounts of calcium and iron. Molasses is an excellent source of both, 1½ tablespoons furnishing approximately one-tenth the estimated daily adult allowance of calcium and one-fifth the estimated daily

25. Burkhardt, L. and Lineberry, R. A.: Determination of Vitamin C and Its Sampling Variation in Strawberries, *Food Research* 7: 332-337, 1942.

adult need of iron. Sorghum supplies a lesser amount of calcium and about an equal amount of iron. Table blend syrups contain a significant but lesser amount of iron.

VEGETABLE OILS

Cottonseed, corn, soybean, peanut and olive oils and in lesser amounts other vegetable oils are consumed as shortenings, salad oils and margarines. The oils as such are sources only of energy. Many oleomargarines are now fortified with 9,000 international units of vitamin A per pound; they also supply some vitamin D.

CHAPTER XIII

FOODS OF ANIMAL ORIGIN

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NATURAL AND ECONOMIC RELATIONSHIPS

Grouped according to natural relationships and then arranged in descending order of economic prominence, the chief types of food of animal origin are as follows:

1. Meats, including fish and poultry, which together command about one fourth¹ of the average American expenditure for food.

2. Milk in its various forms, including cheese, cream and ice cream, representing usually one tenth to one-eighth of the food budget.

3. Butter and other animal fats, about one tenth.

4. Eggs, about one twentieth.

5. Shellfish, which occupy but a small place in the nation's food budget but lend interest to variations in the dietary.

While this sketch will be systematized largely in terms of this fivefold grouping of its subject matter, it will also be possible to avoid repetition by arranging the discussion according to successive aspects of nutritive value.

PHYSICAL STRUCTURE, PROXIMATE COMPOSITION, PROTEIN AND ENERGY VALUES IN NUTRITION

Meats, Poultry and Fish.—In recent years pork has somewhat outranked beef in the American food supply, with lamb and mutton occupying a place far below that of beef and veal. The slaughtering of the meat animals of these three species is a highly centralized industry in the sense that a large proportion of the animals raised for meat are slaughtered in large establishments.

In the case of swine the head is left on the dressed carcass, while with cattle, sheep and lambs the head is removed and the dressed carcass divided longitudinally by splitting the backbone. For this reason and

1. Here and elsewhere such quantitative statements are to be somewhat flexibly construed, because in food statistics the fat meats are sometimes included under meats and sometimes under fats.

also because of greater fatness the dressed weight of swine is about 80 per cent of the live weight; of beef it is about 60 per cent; of lamb and mutton, about 45 to 50 per cent. Of the butcher's meat about 97 to 98 per cent is muscle, with its accompanying adipose tissue and bone, and only about 2 to 3 per cent is liver. That there is no way of increasing the ratio of liver to muscle meat is of course an obvious fact yet one which often seems to be forgotten when liver is emphasized as a food. Liver can never take a large part in the general food supply; its importance in dietetics lies in getting it consumed by the patients who specifically need it rather than in teaching other people to want it.

The proximate composition and energy value for each sufficiently important food of animal origin is given in table 1, based on the recent government compilation of such data for these and other American food materials.²

Market classes and grades of beef and lamb relate to physical properties of the meat which, except as fat affects both, have little if any nutritional significance. Such conventional preferences should be rescrutinized from time to time in the light of newer knowledge: for example, the fashion has been to prefer that meat fat be firm and white, whereas we now know that a softer, yellower meat-fat is apt to be superior nutritionally.

The muscle tissue, considered separately from all deposited fat, i. e. "clear lean" meat, is of fairly constant composition: about 1 per cent of total mineral matter, 20 to 25 per cent of protein and the rest water. There is somewhat less protein and more water in the muscle tissue of fish than of land animals, and in young than in mature animals of a given species; but among the meats and fish ordinarily entering into the human dietary the latter differences are not of such degree as to have much effect on nutritive values.

The outstanding source of difference in the nutritional character of meats is the widely varying proportion of fat. The fatty layers, or masses or adipose tissues, of meat may be thought of as similar in composition to butter: 80 to 90 per cent of actual fat, with about 15 per cent of water, small amounts of protein and salts.

2. Chatfield, Charlotte, and Adams, Georgian: Proximate Composition of American Food Materials. Circular 549, U. S. Dept. Agriculture, June 1940.

The approximate average percentages of protein and fat have been determined for many kinds and cuts of meat as illustrated in table 1.

This table also shows the proximate composition and energy values of the other chief foods of animal origin.

In composition and energy value there is no distinct gap between the fat meats and the commercial fats. Fat pork is, in fact, sometimes grouped with meats and sometimes with fats. If this is kept in mind it will clear up some apparent discrepancies in food statistics.

Eggs, like lean meats, are about three fourths water, with about 1 per cent of mineral matter; but the organic matter for the egg as a whole consists about equally of protein and fat. Egg white is about seven eighths water and one eighth protein, while egg yolk is about one half water, one third fat and one sixth protein.

The actual averages of these constituents for all the foods here mentioned as well as other foods of animal origin, as officially published by the U. S. Department of Agriculture, are given in table 1.

Milk, Cream and Cheese.—While none of the staple meats contain any significant amount of carbohydrate, milk contains more of lactose than of either protein or fat. Milk is also much more watery than even the leanest meat, the latter having about one fourth solids while fresh whole milk has only about one eighth, and fat free milk (the analogue of clear lean meat) is about nine tenths water and one tenth solids.

Cream differs from milk simply in containing more of the fat globules with a consequent (relatively small) diminution of the watery part (aqueous phase) of the milk in which its carbohydrate (lactose, milk sugar) is dissolved and in which its proteins and mineral matters are partly dissolved and partly held in aqueous dispersion. The fat globules constitute one part in 25 or 30 of average whole milk. Hence cream containing, say, five or six times as much fat as milk does, will still contain four fifths to five sixths as much as milk does of all the other milk constituents. Enrichment of the dietary in these milk constituents is often nutritionally desirable. It is therefore important to remember that, if milk itself is not relished, cream may be used instead.

Cheese is another form of milk which may be more interesting to the consumer than the milk itself. In

TABLE 1—*Proximate Composition of American Food Materials*

Food	Basis	As Purchased, per Cent	Constituents of the Edible Portion					Fuel Value	
			Water, per Cent	Protein, per Cent	Fat, per Cent	Ash, per Cent	Total Carbohyrates, per 100 Grams	Calories per 100 Grams	Pound
Bacon, raw, lean	E P	8	29	12.2	53	4.7	(1.4)	531	2,410
	A P		26	11.2	49	4.5	(1.0)	483	2,220
Bacon, raw, medium	E P	6	20	9.1	65	4.3	(1.1)	636	2,840
	A P		19	8.6	61	4.0	(1.0)	588	2,670
Bacon, raw, fat	E P		13	6.2	76	3.8	(0.7)	712	3,230
	A P	4	10	6.0	73	3.6	(0.7)	683	3,100
Bacon, broiled	F P		13	20	50	6	1	599	2,720
Bass, Atlantic black sea, raw	E P		79.3	19.2	1.5	1.2	0	85	380
	A P	61	30.9	7.5	0.0	0.0	0	34	155
Bass, black, large and small mouthed raw	E P		76.7	20.6	1.8	1.2	0	99	445
	A P	56	33.7	9.1	0.8	0.5	0	43	195
Bass, California white sea, raw	E P		76.3	21.4	0.0	1.4	0	90	410
Bass striped, raw	E P		77.7	18.9	2.7	1.2	0	100	455
	A P	57	33.4	8.1	1.5	0.5	0	43	185
Bass, striped, raw, entrails removed	A P	51	38.1	9.3	1	0.6	0	49	220
Beef, fresh, carcass or sides including kidney fat	E P		66	18.8	14	0.97	0	201	910
Thin (common grade)	A P	19	54	15.5	11	0.8	0	163	740
Medium (medium grade)	E P		60	17.5	22	0.87	0	268	1,220
	A P	16	50	14.7	18	0.7	0	225	1,020
Fat (good grade)	E P		50	16.8	28	0.79	0	317	1,440
	A P	10	47	13.9	24	0.7	0	270	1,220
Very fat (choice and prime grades)	E P		47	13.7	39	0.65	0	406	1,840
	A P	12	41	12.1	34	0.6	0	357	1,620
Wholesale cuts	E P		71	19.2	9	0.94	0	158	720
Chuck, thin	A P	19	57	15.6	7	0.8	0	128	580
Chuck, medium	E P		60	18.6	16	0.88	0	218	990
	A P	17	54	15.4	13	0.7	0	181	820
Chuck, fat	E P		60	17.6	22	0.82	0	268	1,220
	A P	15	51	15.0	19	0.7	0	228	1,060

Chuck, very fat	E P	52	15 0	32	0 74	0	348	1,580
	A P	13	13 0	28	0 6	0	303	1,370
Flank, thin	E P	52	17 0	30	0 77	0	338	1,530
	A P	1	16 8	30	0 76	0	335	1,520
Flank, medium	E P	45	14 6	40	0 64	0	418	1,900
	A P	1	14 5	40	0 63	0	414	1,880
Flank, fat	E P	39	12 7	48	0 54	0	483	2,190
	A P	1	12 6	48	0 53	0	478	2,170
Flank, very fat	E P	28	9 3	62	0 36	0	595	2,700
	A P	28	9 2	61	0 36	0	589	2,670
Kidney fat (suet)	E P	9	3 0	88	0 16	0	804	3,650
Medium	E P	7	1 7	93	0 12	0	844	3,830
Fat	E P	4	1 5	94	0 11	0	852	3,860
Very fat	E P	4	1 5	94	0 11	0	852	3,860
Loon, excluding kidney knob	F P	64	18 6	16	0 95	0	218	990
Thin	A P	54	15 6	13	0 8	0	183	830
Medium	E P	57	16 9	25	0 84	0	293	1,330
	A P	49	14 5	22	0 7	0	252	1,140
Fat	E P	53	15 6	31	0 77	0	341	1,550
	A P	46	13 7	27	0 7	0	300	1,360
Very fat	E P	44	12 8	43	0 62	0	438	1,990
	A P	39	11 5	39	0 6	0	394	1,790
Neck, thin	E P	69	19 1	11	0 92	0	175	800
	A P	50	13 9	8	0 7	0	128	580
Neck, medium	E P	62	18 2	19	0 85	0	244	1,110
	A P	46	13 5	14	0 6	0	180	820
Neck, fat	E P	57	17 0	25	0 80	0	293	1,330
	A P	43	12 8	19	0 6	0	220	1,000
Neck, very fat	E P	50	14 0	35	0 71	0	371	1,680
	A P	38	10 6	27	0 5	0	282	1,280
Plate and brisket, thin	E P	60	17 9	21	0 87	0	261	1,180
	A P	47	14 0	16	0 7	0	203	920
Plate and brisket, medium	E P	53	15 8	30	0 75	0	333	1,510
	A P	44	13 0	25	0 6	0	273	1,240
Plate and brisket, fat	E P	47	14 0	38	0 65	0	398	1,810
	A P	40	11 9	32	0 6	0	338	1,530
Plate and brisket, very fat	E P	38	11 0	51	0 48	0	508	2,280
	A P	33	9 8	45	0 4	0	448	2,080

TABLE 1.—Proximate Composition of American Food Materials—Continued

Food	As Purchased: Refuse, per Cent	Constituents of the Edible Portion					Fuel Value	
		Water, per Cent	Protein, per Cent	Fat, per Cent	Ash, per Cent	Total Carbohy- drates, per Cent	Calories per 100 Grams	Calories per Pound
Beef, fresh, carcass or sides, including kidney fat— Wholesale cuts—Continued								
Rib, thin	25	66	19.0	14	0.94	0	202	920
		50	14.2	10	0.7	0	152	650
Rib, medium	21	59	17.4	23	0.83	0	277	1,250
		46	13.7	18	0.7	0	219	960
Rib, fat	18	52	15.8	31	0.74	0	342	1,550
		43	13.0	25	0.6	0	281	1,270
Rib, very fat.	14	43	12.7	44	0.59	0	447	2,080
		37	10.9	38	0.5	0	384	1,740
Round, thin	12	71	19.7	8	1.00	0	151	680
		63	17.3	7	0.9	0	133	600
Round, medium ..	11	67	19.3	13	0.95	0	194	880
		59	17.2	12	0.8	0	173	780
Round, fat	10	63	18.7	17	0.90	0	228	1,000
		57	16.8	15	0.8	0	205	930
Round, very fat....	9	58	17.4	24	0.82	0	286	1,300
		53	15.8	22	0.7	0	260	1,180
Rump, thin	27	60	17.4	22	0.88	0	268	1,210
		44	12.7	16	0.6	0	185	860
Rump, medium ..	24	53	15.5	31	0.77	0	341	1,550
		40	11.8	24	0.6	0	259	1,180
Rump, fat	22	48	14.2	37	0.69	0	390	1,770
		38	11.1	29	0.5	0	304	1,380
Rump, very fat..	19	40	11.4	48	0.56	0	478	2,170
		32	9.2	39	0.5	0	367	1,700
Shank, fore, thin ..	41	72	21.0	6	0.98	0	138	630
		42	12.4	4	0.6	0	81	370
Shank, fore, medium ..	41	70	20.4	9	0.94	0	163	740
		41	12.0	5	0.6	0	96	440
Shank, fore, fat....	40	67	19.7	12	0.90	0	187	850
		40	11.8	7	0.5	0	112	510

Shank, fore, very fat.....	E. P.	63	18.2	18	0.83	0	235	1,070
Shank, hind, thin.....	A. P.	39	11.3	11	0.5	0	146	690
Shank, hind, medium.....	E. P.	71	20.8	7	0.96	0	146	690
Shank, hind, fat.....	A. P.	29	8.5	3	0.4	0	60	270
Shank, hind, very fat.....	E. P.	69	20.1	10	0.93	0	170	770
Shank, hind, very fat.....	A. P.	28	8.2	4	0.4	0	70	320
Shank, hind, very fat.....	E. P.	66	19.2	14	0.88	0	203	920
Shank, hind, very fat.....	A. P.	28	8.3	6	0.4	0	87	400
Shank, hind, very fat.....	E. P.	59	17.1	23	0.76	0	275	1,250
Shank, hind, very fat.....	A. P.	27	7.7	10	0.3	0	124	560
Beef, canned, corned beef hash.....	E. P.	70.7	12.8	5.5	2.3	8.7	136	610
Beef, canned, roast beef.....	E. P.	60	25	13	2	0	217	980
Beef, corned, very lean.....	E. P.	65.4	19.4	8	0.2	0	150	680
Beef, corned, lean.....	E. P.	62.8	18.4	13	5.8	0	191	860
Beef, corned, medium.....	E. P.	54.2	15.8	25	5.0	0	288	1,310
Beef, corned, fat.....	E. P.	46.2	13.5	36	4.3	0	378	1,710
Beef, corned, canned, lean.....	E. P.	62.0	26.4	8	3.6	0	178	810
Beef, corned, canned, medium.....	E. P.	59.3	25.3	12	3.4	0	209	950
Beef, corned, canned, fat.....	E. P.	55.3	23.5	18	3.2	0	256	1,160
Beef, dried (salted and smoked).....	E. P.	47.7	34.3	6.3	11.6	0	184	880
Bluefish or talior, raw.....	E. P.	74.6	20.5	4.0	1.2	0	118	535
Bluefish or talior, raw, whole or entrails removed....	A. P.	38.0	10.5	2.0	0.6	0	60	275
Bonito, including California, Atlantic, and striped, raw.....	E. P.	67.6	24.0	7.3	1.4	0	102	735
Bonito, including California, Atlantic, and striped, raw.....	A. P.	39.2	13.9	4.2	0.8	0	91	425
Bouillon	E. P.	95	(1)	0	1.5	(0)	4	20
Bouillon cubes	E. P.	5	(6)	2.5	68	(0)	46	210
Brains, fresh, beef	E. P.	77.9	10.5	8.8	1.4	1.4	127	580
Brains, fresh, calf	E. P.	80.6	10.0	8.3	1.3	0	115	520
Brains, fresh, hog	E. P.	78.2	10.6	9.0	1.5	0.7	126	570
Brains, fresh, sheep	E. P.	78.8	10.5	8.3	1.4	1.0	121	550
Butter	E. P.	15.5	0.6	81.0	2.5	0.4	783	3,325
Butterfish or dollarfish, raw.....	E. P.	71.4	18.1	10.2	1.4	0	164	745
Butterfish or dollarfish, raw.....	A. P.	36.4	9.2	5.2	0.7	0	84	380

TABLE 1.—Proximate Composition of American Food Materials—Continued

Food	As Purchased: Refuse, per Cent	Constituents of the Edible Portion					Fuel Value	
		Water, per Cent	Protein, per Cent	Fat, per Cent	Ash, per Cent	Total Carbohy- drates, per Cent	Calories per 100 Grams	Calories per Pound
Buttermilk, genuine	90.7	3.5	0.5	0.7	4.6	37	165
Buttermilk, artificially cultured.....	..	90.5	3.5	0.2	0.8	5.0	36	160
Carp or German carp, raw.....	..	77.9	18.2	2.2	1.2	0	93	430
Carp sucker, raw.....	..	76.2	19.2	3.2	1.2	0	106	480
.....	61	89.7	7.5	1.2	0.5	0	41	185
Caviar, sturgeon, granular.....	..	46.0	26.9	15.0	8.8	(0)	243	1,100
Caviar, sturgeon, pressed.....	..	36.0	34.4	16.7	8.0	(0)	288	1,305
Cheese, Camembert	51.0	19.7	25.2	4.1	.0	306	1,385
Cheese, Cheddar, American.....	..	39	23.9	32.3	3.1	1.7	393	1,785
Cheese, Cheddar, processed.....	..	40	22.3	30.2	5.8	1.7	368	1,670
Cheese, cottage (from skim milk).....	..	74.0	19.2	0.8	1.7	4.8	101	460
Cheese, cream (Neufchâtel type).....	..	53.3	7.1	36.9	1.0	1.7	367	1,665
Cheese, Edam	43.3	27.0	20.1	5.6	4.0	305	1,386
Cheese, Emmentaler (similar to Swiss)	..							
Cheese, Gruyere (similar to Swiss)	..							
Cheese, Liederkranz	53.3	15.8	25.6	4.2	1.1	298	1,350
Cheese, Limburger	38.3	23.5	32.4	5.1	0.7	388	1,760
Cheese, Limburger, processed.....	..	48	21.2	26.4	3.7	0.7	325	1,475
Cheese, Mynost	28.3	9.3	1.4	6.6	54.4	267	1,215
Cheese, Parmesan	28.9	36.3	27.4	5.1	2.3	401	1,890
Cheese, Roquefort	37.4	21.7	33.2	6.3	1.4	391	1,775
Cheese, Swiss	34.0	28.6	31.3	4.2	1.9	404	1,830
Cheese, Swiss, processed.....	..	42	23.8	26.1	6.5	1.6	336	1,595
Chicken, fresh								
Squab broilers (%-1% lb. live weight)								
Total edible	74.9	21.6	2.7	1.4	0	111	500
Live	58	31.5	9.1	1.1	0.6	0	46	210
Dressed	52	36.0	10.4	1.3	0.7	0	53	240
Drawn	32	50.9	14.7	1.8	1.0	0	75	340

[illegible]

TABLE 1.—Proximate Composition of American Food Materials—Continued

Food	Basis	As Purchased: Refuse, per Cent	Constituents of the Edible Portion					Fuel Value	
			Water, per Cent	Protein, per Cent	Fat, per Cent	Ash, per Cent	Total Carbohyrates, Grams	Calories per 100 Grams	Calories per Pound
Flesh, fat, and skin.....	E. P.	..	55.8	21.6	22.0	1.2	0	284	1,290
Live.....	A. P.	51	27.3	10.6	10.8	0.6	0	139	630
Dressed.....	A. P.	46	30.1	11.7	11.9	0.6	0	154	700
Drawn.....	A. P.	33	37.4	14.5	14.7	0.8	0	191	860
All classes, light meat only.....	E. P.	..	72.5	23.3	3.2	1.2	0	122	550
All classes, dark meat only.....	E. P.	..	73.0	21.0	4.7	1.1	0	126	570
Canned, meat only.....	E. P.	..	61.9	29.8	8.0	2.4	0	191	870
Canned, meat and broth.....	E. P.	..	70.3	23.2	3.4	1.6	0	123	560
Cooked (see Meat and Poultry, cooked)									
Potted.....	E. P.	..	58.2	18.8	18.8	2.6	0	244	1,110
Clams, fresh, long, meat only.....	E. P.	..	80.6	13.6	1.7	2.0	2.1	78	355
Clams, fresh, long, meat and liquor: (59% solids, 41% liquor)	A. P.	65	28.2	4.8	0.6	0.7	0.7	27	125
Clams, fresh, round, meat only.....	E. P.	..	85.8	8.6	1.0	2.6	2.0	51	235
Clams, fresh, round, meat only.....	A. P.	42	49.8	5.0	0.6	1.5	1.2	30	135
Clams, fresh, round, meat and liquor (52% solids; 48% liquor)	E. P.	..	79.8	11.1	0.9	2.3	5.9	76	345
Clams, fresh, round, meat and liquor (52% solids; 48% liquor)	A. P.	83	13.6	1.9	0.2	0.4	0.9	13	60
Clams, fresh, long and round, meat only.....	E. P.	..	86.2	6.5	0.4	2.7	4.2	46	210
Clams, fresh, long and round, meat and liquor (56% solids; 44% liquor)	A. P.	68	27.6	2.1	0.1	0.9	2.1	15	65
Clams, canned, long and round, meat only (discarding liquor)	E. P.	..	80.3	12.8	1.4	2.1	3.4	77	350
Clams, canned, long and round, meat only (discarding liquor)	E. P.	..	86.9	8.1	0.9	2.6	2.5	50	230
Clams, canned, long and round, liquor.....	E. P.	..	76.8	15.8	2.5	2.8	2.1	94	425
Clams, canned, long and round, meat and liquor.....	A. P.	59	31.5	6.5	1.0	1.1	0.9	39	175
Clam bouillon, juice or nectar, canned.....	E. P.	..	93.7	2.2	0.1	1.9	2.1	18	80
Od, raw.....	E. P.	..	86.7	7.9	1	2.3	2.1	49	220
Od, raw, whole.....	E. P.	..	94.8	1.4	.0	2.3	1.5	12	55
Od, raw, dressed.....	E. P.	..	82.6	16.5	0.4	1.2	0	70	315
Od, raw, steaks.....	A. P.	52	39.6	7.9	0.2	0.6	0	33	150
Od, canned (see Cod, raw, E. P.)	A. P.	31	37.0	11.4	0.3	0.8	0	43	220
		9	75.2	15.0	0.4	1.1	0	63	285

[illegible]

TABLE 1.—*Proximate Composition of American Food Materials—Continued*

Food	Basis	As Pur- chased: Refuse, per Cent	Constituents of the Edible Portion					Fuel Value	
			Water, per Cent	Protein, per Cent	Fat, per Cent	Ash, per Cent	Total Carbo- hydrates, per Cent	Calories per 100 Grams	Calories per Pound
Lamb, fresh, rib cut (9 ribs), medium fat.	E. P.	..	51.9	14.9	32.4	0.8	0	351	1,590
Lamb, fresh, shoulder (3 ribs), medium fat.	A. P.	24	39.4	11.3	24.6	0.6	0	267	1,210
Lamb, fresh, shoulder (3 ribs), medium fat.	E. P.	..	58.3	15.6	25.3	0.8	0	290	1,320
Lamb, fresh, shoulder (3 ribs), medium fat.	A. P.	20	46.6	12.5	20.2	0.6	0	232	1,050
Lamb, fresh, cooked (see Meat and Poultry, cooked)									
Lard	E. P.	100	900	4,080
Liver, fresh, beef.	E. P.	..	69.7	19.7	3.2	1.4	6.0	132	600
Liver, fresh, calf.	E. P.	..	70.8	19.0	4.9	1.3	4.0	136	630
Liver, fresh, hog.	E. P.	..	72.3	19.7	4.8	1.5	1.7	129	590
Liver, fresh, sheep or lamb.	E. P.	..	70.8	21.0	3.9	1.4	2.9	131	590
Meat and poultry, cooked									
Lean, medium done.	E. P.	..	63	30	6	1.2	0	174	790
Medium fat, medium done.	E. P.	..	54	27	18	1.1	0	270	1,220
Fat, medium done.	E. P.	..	47	22	30	0.9	0	358	1,620
Very fat, medium done.	E. P.	..	37	17	45	0.7	0	473	2,150
Milk, cow, fresh, whole.	E. P.	..	87.0	3.5	3.9	0.7	4.9	69	310
Milk, cow, fresh, skim.	E. P.	..	90.5	3.5	0.2	0.8	5.0	160	160
Milk, cow, canned, evaporated (unsweetened).	E. P.	..	73.7	7.0	7.9	1.5	9.9	139	630
Milk, cow, canned, condensed (sweetened).	E. P.	..	47.0	8.1	8.4	1.7	54.8	327	1,485
Milk, cow, dry, skim.	E. P.	..	3.5	35.6	1.0	7.9	52.0	359	1,630
Milk, cow, dry, whole.	E. P.	..	3.5	25.8	26.7	6.0	38.0	496	2,250
Milk, cow, malted, plain.	E. P.	..	2.6	14.6	8.5	3.6	70.7	418	1,865
Milk, goat, fresh.	E. P.	..	87.0	3.3	4.2	0.7	4.8	70	320
Milk, human, fresh.	E. P.	..	87.5	1.4	3.7	0.2	7.2	68	305
Oleomargarine.	E. P.	..	15.5	0.6	81	2.5	0.4	783	3,325
Oysters, fresh, solids only.	E. P.	..	80.3	9.8	2.0	2.0	5.9	81	365
Oysters, fresh, solids and liquor (55% solids; 45% liquor)	A. P.	90	8.0	1.0	0.2	0.2	0.6	8	35
Oysters, fresh, solids and liquor (55% solids; 45% liquor)	E. P.	..	87.1	6.0	1.2	2.0	3.7	50	225
Oysters, fresh, solids and liquor (55% solids; 45% liquor)	A. P.	82	15.7	1.1	0.2	0.4	0.6	9	40

Oysters, canned, drained solids.....	E. P.	..	80.3	9.8	2.0	2.0	6.9	81	365
Oysters, canned, solids and liquid.....	E. P.	..	87.1	6.0	1.2	2.0	3.7	50	225
Porkey, Atlantic, or foilhead, raw.....	E. P.	..	76.2	21.4	0.9	1.5	0	94	425
	A. P.	50	38.1	10.7	0.4	0.8	0	47	210
Pork, fresh, raw									
Carcass or side, thin.....	E. P.	..	50	14.1	35	0.8	0	371	1,690
	A. P.	18	41	11.6	29	0.6	0	305	1,380
Carcass or side, medium.....	E. P.	..	42	11.9	45	0.6	0	453	2,060
	A. P.	12	37	10.5	40	0.6	0	398	1,810
Carcass or side, fat.....	E. P.	..	35	9.8	55	0.5	0	534	2,420
	A. P.	10	31	8.8	50	0.5	0	481	2,180
Pork, cured, raw									
Ham, smoked, very lean (also Canadian bacon)..	E. P.	..	56	22.1	15	6.2	(0.3)	225	1,020
Ham, smoked, lean.....	E. P.	..	49	19.5	25	5.8	(0.3)	304	1,380
	A. P.	14	42	16.8	22	5.0	(0.3)	262	1,190
Ham, smoked, medium.	E. P.	..	42	16.9	35	5.4	(0.3)	384	1,740
	A. P.	13	37	14.7	30	4.7	(0.3)	324	1,510
Ham, smoked, fat.....	E. P.	..	36	14.6	44	5.1	(0.3)	456	2,070
	A. P.	11	32	13.0	39	4.5	(0.3)	405	1,840
Shoulder, smoked, lean....	E. P.	..	42	16.9	35	5.4	(0.3)	384	1,740
	A. P.	14	36	14.5	30	4.6	(0.3)	330	1,500
Shoulder, smoked, medium.....	E. P.	..	36	14.6	44	5.1	(0.3)	456	2,070
	A. P.	12	32	12.8	39	4.5	(0.3)	401	1,820
Shoulder, smoked, fat.....	E. P.	..	30	12.2	63	4.7	(0.3)	527	2,390
	A. P.	10	27	11.0	48	4.2	(0.3)	474	2,150
Roe, fish, fresh (including carp, shad, herring, salmon)	E. P.	..	66.8	26.2	3.1	1.6	(0.)	133	600
Salmon, canned	E. P.	..	67.4	20.6	9.6	2.4	0	169	765
	A. P.	2	66.1	20.2	9.4	2.0	0	165	750
Sausage, beef and pork.....	E. P.	..	44.8	11.3	41.2	2.5	0	416	1,890
Scallops, fresh	E. P.	..	80.3	14.8	0.1	1.4	3.4	74	335
Swordfish, raw	E. P.	..	74.9	18.8	4.4	1.5	0	115	520
Tuna, canned	E. P.	..	63.1	24.2	10.8	2.0	0	194	890
Turkey, fresh, medium fat birds, total edible.....	E. P.	..	58.3	20.1	20.2	1.0	0	262	1,190
Veal, fresh, carcass or sides, excluding kidney and kidney fat, thin	E. P.	..	71	19.7	8	1.0	0	151	690
	A. P.	23	55	15.2	6	0.8	0	116	530
Veal, fresh, carcass or sides, excluding kidney and kidney fat, medium	E. P.	..	68	19.1	12	1.0	0	184	840
	A. P.	21	54	15.1	9	0.8	0	146	660
Veal, fresh, carcass or sides, excluding kidney and kidney fat, fat	E. P.	..	65	18.5	16	0.9	0	218	990
	A. P.	19	52	15.0	13	0.7	0	177	800

general, an ounce of cheese is equivalent to a pint of milk, though of course most of the lactose, certain fractions of the protein, mineral and vitamin values have escaped in the whey. The cheese retains, however, nearly all of the fat and fat soluble vitamins of the milk and much the greater part of the protein, the calcium and the riboflavin. (All this, of course, refers to real cheese, not cottage cheese, which retains very much less of the mineral and vitamin values.)

Shellfish share with milk the property of containing a significant percentage of carbohydrate (in their case, glycogen); but otherwise their composition resembles that of meats, fish and poultry.

MINERAL ELEMENTS AND THEIR NUTRITIONAL AVAILABILITY

Statements regarding the nutritional characteristics and nutritive values of meats are complicated (and may become confused or misleading) by the wide differences in fatness and resulting chemical composition among meats. This is true not only as between different species used as human food but also as between different individuals of the same species (and even of the same sex and age) and often as between different cuts from the same carcass.

Considered aside from the glandular organs and from bone, meats may be regarded as essentially composed of muscle tissue and adipose tissue, but these in quite variable proportions (quantitative relations).

Relatively few samples of meat have been analyzed for individual mineral elements. These have been chiefly clear lean specimens because it has been considered and is doubtless true that the mineral elements, like the proteins, belong essentially to the protoplasmic part of the meat. From the same point of view it may be expected that, as far as the influence of the varying amounts of fat on the mineral values of the meat are concerned, the amounts of the mineral elements will run essentially parallel with the amounts of protein. Hence in calculating the nutritive values of dietaries or larger food supplies one may, after computing the total meat protein from such data as those in table 1, then estimate the mineral contents by relation to the protein, using conventional average figures such as those given for meats and fish separately in table 2. For

comparison table 2³ shows the amounts of the chief mineral elements for milk and for eggs as well as for meats and for fish, each per hundred grams of protein in the respective food.

Especially in the case of the iron contents of meats it was never intended to imply that the approximate average relationship indicated in table 2 should hold good for each different organ and tissue. Forbes and Swift⁴ have published the results of their determinations of iron in 18 individual samples of meat (and a sample of blood). These results are here reprinted, by permission, as table 3.

When account is taken of the relative quantities in which the different kinds of meat enter into the Ameri-

TABLE 2.—*Approximate Average Relationships of Mineral Elements to Protein in the Chief Types of Food of Animal Origin*

	Grams of the Mineral Element per Hundred Grams of Protein			
	Meats	Fish	Eggs	Milk
Calcium	0.058	0.109	0.453	3.372
Magnesium.....	0.118	0.183	0.101	0.343
Potassium.....	1.694	1.671	1.078	4.086
Sodium.....	0.421	0.373	1.094	1.457
Phosphorus.....	1.078	1.148	1.750	2.657
Chlorine.....	0.378	0.528	0.938	3.028
Sulfur.....	1.146	1.119	1.539	0.971
Iron.....	0.015	0.0055	0.024	0.0057

can food supply, the data for iron in tables 2 and 3 are seen to be quite consistent.

Less consistent are the published findings as to the nutritional availability of the iron of meats. Even the papers of such eminent investigators as Whipple and Elvehjem give such divergent impressions that it seems still an open question whether the different methods commonly accepted as indicative of the relative quantitative utilization of food iron in nutrition should be considered as measuring availability in the same (or in any closely comparable) sense. Numerical expres-

3. By permission of the Macmillan Company, publishers, the data here given are in part taken from pages 563 and 564 of Sherman's *Chemistry of Food and Nutrition*, ed. 6, May 1941, and in part adapted from the extensive table of which those pages are a part.

4. Forbes, E. B., and Swift, R. W.: *Iron Content of Meats*, J. Biol. Chem. 67:517 (Feb.) 1926.

sions of availability or utilization of meat iron in nutrition are therefore omitted here lest they should confuse instead of clarifying the subject.

We know of no reason for doubting the nutritional availability of the other mineral elements of meats and of all the mineral elements of milk and eggs.

VITAMIN VALUES

The vitamin A value of a dietary, and of most of the individual foods of animal origin, is due (1) to

TABLE 3.—*Composition of Meat Samples (Forbes and Swift)*

Sam- ple No.	Kind of Meat	Iron, per Cent	Nitro- gen, per Cent	Protein (N × 6.25), per Cent	Ether Ex- tract, per Cent	Mois- ture, per Cent	Mg. Iron per 100 Gm. of Pro- tein
105	Bacon, cured.....	0.0013	1.67	10.44	64.10	22.31	12.5
107	Ham, cured.....	0.0014	3.37	21.06	13.60	64.61	6.0
114	Pork shoulder... ..	0.0015	2.93	18.31	14.41	67.14	8.2
106	Pork hind quarter...	0.0015	3.14	19.63	10.54	69.07	7.6
112	Lamb shoulder.....	0.0016	3.01	18.81	6.94	72.95	8.5
113	Lamb hind quarter..	0.0016	3.25	20.31	5.27	75.59	7.9
102	Beef rib.....	0.0024	3.24	20.25	6.05	72.70	11.9
100	Beef round.....	0.0025	3.55	22.19	3.48	74.65	11.3
101	Beef loin.....	0.0025	3.29	20.56	6.39	72.02	12.2
103	Beef chuck.....	0.0025	3.17	19.81	7.13	72.84	12.6
109	Veal fore quarter....	0.0023	3.47	21.69	1.70	76.08	10.6
110	Veal hind quarter....	0.0027	3.54	22.13	1.54	76.68	12.2
116	Veal kidney.....	0.0040	2.61	16.31	4.17	77.82	24.5
111	Beef heart.....	0.0044	2.59	16.19	4.94	78.91	27.2
117	Beef brain.....	0.0053	1.68	10.50	7.89	79.15	50.5
104	Beef liver.....	0.0082	3.30	20.63	4.66	68.33	39.7
115	Beef spleen.....	0.0138	3.03	18.94	1.90	77.50	72.9
108	Beef kidney.....	0.0188	2.58	16.13	1.85	78.67	116.6
118	Beef blood.....	0.0444	2.87	17.94	80.99	247.5

vitamin A itself and (2) to its precursors, which are formed in plants and to some extent are stored in the animal body, where, however, the greater part is changed into vitamin A. Corresponding with the nutritional importance of vitamin A we find that evolution has accentuated the property of transfer of this vitamin from one generation to the next through milk and eggs. Most of the vitamin A which the body itself retains is held in the liver, whose content of this and other vitamins thus varies so greatly with the individual nutritional background as to make it seem nearly meaningless and perhaps misleading to attempt numerical averages in table 4. Taking account of

available quantities, milk (including cheese, cream and ice cream), butter, margarines enriched with vitamin A from fish liver oils, the fish oils themselves and eggs are the chief sources of animal origin.

Of the B vitamin group our knowledge is as yet very uneven. Approximate average thiamine and riboflavin contents of typical foods of animal origin, based on a study of all the data available to June 1942 (including unpublished findings consulted through the courtesy of Dr. C. N. Frey, Dr. R. R. Williams and

TABLE 4.—*Approximate Average Vitamin Values of Some Typical Foods of Animal Origin*

Food	Data to May 1942		
	Vitamin A Value, International Units per 100 Gm.	Thiamine, Micrograms per 100 Gm.	Riboflavin, Micrograms per 100 Gm.
Pork, lean.....	Negligible	900	240
Bacon, medium fat, raw.....	Negligible	100	100
Beef, clear lean, raw.....	Negligible	160	230
Lamb, lean, raw.....	Negligible	200	235
Chicken, dark meat.....	Negligible	200 ?	260
Chicken, light meat.....	Negligible	200 ?	60
Eggs.....	1,500	150	350
Egg white.....	Traces	Traces	250
Egg yolk.....	4,000	400	550
Milk.....	195	50	205
Cream (24% fat).....	1,500	40	160
Ice cream (13% fat).....	800	50	200
Cheese (32% fat).....	2,200	40	500
Butter.....	4,500	Negligible	Negligible
Oysters.....	200	250	Undetermined
Milk, dried, skim.....	Undetermined	500	2,000

Dr. V. H. Cheldelin, as well as my co-workers at Columbia) are given in table 4. Lean meats, eggs, milk, cheese, cream and ice cream are all noteworthy sources of riboflavin when taken in the quantities which are normal to typical American dietaries. In such dietaries, milk and its products will furnish something like one half of the total riboflavin, and meat and eggs the greater part of the remainder. Of thiamine the foods of animal origin are not such prominent contributors, a relatively larger share of the responsibility for the thiamine intake resting on enriched and whole grain breadstuffs and cereals. Lean pork is richer in thiamine than other common meats.

Niacin (nicotinic acid) is qualitatively well established as an antipellagric factor; but the estimates of quantities of niacin contained in foods or concerned in nutrition are as yet very tentative and uncertain, and it is a mistake (though doubtless one for which we scientists are ourselves responsible) to suppose that niacin bears any such clearcut relation to pellagra as, e. g., ascorbic acid bears to scurvy. On paper, pellagra may have been redefined as nicotinic acid deficiency, but the typical pellagrin actually needs so much more than this one factor that his case is probably not so parallel with that of the blacktongue dog as has often been assumed; and for the same reasons as well as because of the uncertainties of present analytic methods, figures comparing the estimated nicotinic acid contents of foods are apt to give very misleading impressions. Therefore I do not attempt to include them in table 4, or the other B vitamins now recognized but of which our knowledge is as yet little more than qualitative.

From a combined study of the earlier work of Osborne and Mendel and the recent work of Elvehjem and his co-workers at Wisconsin, it appears probable that both milk and meat contain all the B vitamins concerned in mammalian nutrition.

Ascorbic acid has been shown by Bessey and King ⁵ to occur normally in amounts demonstrable by modern methods in animal tissues generally, especially the glandular organs. Muscle, however, contains very little, and this is further reduced by the time the meat is served at table. For the purposes of practical dietetics, therefore, the vitamin C value of meats is considered negligible; also that of eggs. Fresh milk and oysters furnish about 2 to 3 mg. of this vitamin per hundred grams. The extent of the loss in present day pasteurization of milk has been repeatedly found to be about one fifth. In practice we look to fruits and vegetables rather than to the foods of animal origin for our dietary vitamin C.

Vitamin D is present in only negligible amounts in meats generally; slightly more in liver, milk and butter;

5. Bessey, O. A., and King, C. G.: The Distribution of Vitamin C in Plant and Animal Tissues and Its Determination, *J. Biol. Chem.* **103**: 687-698 (Dec.) 1933.

distinctly more in eggs. The amounts contained in these foods have, however, been but little studied, since it has been shown that the fish liver oils contain very much greater concentrations and also that milk can readily be fortified to make the now familiar "vitamin D milk" of commerce.

For the reasons just given, the data on vitamins C and D naturally present in foods of animal origin are omitted from table 4.

Losses of Vitamins in Cooking.—Losses in cooking are usually larger for vitamin C than for any of the other vitamins. Several independent investigations have consistently shown the diminution of 18 to 20 per cent in the vitamin C value of milk in modern pasteurization, and there is no reason to suppose that the loss would be very different in ordinary cooking operations. There has been no occasion for the comparison of different foods of animal origin in this respect, as so few of them have measurable vitamin C value. Cooking losses of thiamine and riboflavin seem to be higher for meat than for milk, with eggs probably occupying an intermediate position but yielding extremely variable results according to the mode and conditions of cooking. The cooking losses of thiamine and riboflavin in meats have also seemed to vary greatly in the investigations thus far reported, and much additional experimental work in this field is now proposed and in some cases in progress. Hence it seems better not to record in numerical form any findings which could now be given, since we may hope that more conclusive data will be available soon.

OTHER DIETARY CONSIDERATIONS

There is experimental evidence, the fuller explanation of which is still under active research, that some fats of animal origin have special values in nutrition beyond those due to the hitherto well established factors. To Dr. Burr in Minnesota and to Dr. Hart in Wisconsin, who with their respective co-workers are outstandingly engaged in two such lines of research, I am indebted for personal communications bringing their findings up to May 1942 as follows: Dr. Burr holds that, while the explanation is still a research problem, a few fats including lard are superior to many other food fats

as shown by growth experiments with young rats; and Dr. Hart writes "Our work with the 21 day old rat supports the conclusion that there are in butter fat saturated fatty acids of high molecular weight which accelerate the rate of growth as compared with such vegetable oils as corn oil, cottonseed oil, soybean oil, coconut oil and olive oil."

While meat, eggs and milk are much alike in the nutritional efficiency of their proteins, yet these are accompanied by other nutrients which in some respects are quite different either in kind or relative amount, with the result that meat and eggs do not assist the body, as does milk, in the maintenance of its alkali reserve and of a favorable intestinal flora, and hygiene of the alimentary tract. Also the larger the proportion in which milk is used as source of animal protein, the better insured is the liberality of calcium intake, which is now known to be more important at all ages than hitherto understood.

Limitation of space forbids discussion here of the relative economy of the different foods of animal origin from the point of view of the percentage of the food-money which is spent for each and its percentage contribution to each of the nutrient factors of the dietary; but this is something which physicians in the future may well carry in mind, now that we know how greatly health depends on the wise investment of the money available for food.

CHAPTER XIV

UNUSUAL FOODS OF HIGH NUTRITIVE VALUE

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AND

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The successful prosecution of this war, as stressed by Herbert Hoover¹ during World War I, imposes a responsibility on the food exporting countries of the world; namely, that of providing adequate supplies of food for themselves and for their allies. There is no practical way to get food to any part of western Europe now except Great Britain without postponing the winning of the war, but when the war is won the additional gigantic problem will arise of finding food for much of Europe and for Asia. It is probable that many hundred million people will be starving then. It is presumed that half the populations of the occupied countries and Spain are starving now.

Vice President Henry Wallace^{1a} has estimated that the wheat in storage in Canada, the United States, Australia and Argentina would cover the import requirements of Europe for nearly three years. The amount of corn on hand is presumably as great. However, wheat and corn alone will not suffice. Excellent as they may be as foods, the newer knowledge of nutrition teaches that several vitamins and some protein fractions which wheat and corn alone cannot supply are needed to provide for adequate nutrition. It teaches, indeed, that providing ample calories in a diet which is limited in certain nutrients intensifies the need for missing nutrients.

A cursory survey of any bibliography on foods reveals that almost every living thing has graced man's bill of fare at one time or another. It also is apparent that primitive peoples, as a rule, have been "fortunate in

1. Hoover, Herbert: *The Food Armies of Liberty: The Winning Weapon—Food*, National Geographic Magazine, September 1917.

1a. Wallace, H. A.: *Foundations of the Peace*, Atlantic Monthly 169: 34-41 (Jan.) 1942.

their food selections.^{1b} The diets of those nations of the world which are most advanced in technological achievement suffer by comparison. Technology directed at the food supply has not been wisely guided, and the result is not a happy one. The dramatic improvement in the death rate throughout the so-called civilized part of the world can only partly be explained by improved nutrition in some sections of these populations. It is mainly due to the application of medical science, especially the application of public health and hygiene. The increasing incidence of degenerative diseases and high incidence of decay of teeth suggest that average vigor in the more civilized races has declined.

The several hundred delegates who attended the Washington Nutrition Conference in May 1941 approved recommendations relating to requirements for good nutrition submitted by the Food and Nutrition Board of the National Research Council. These recommendations were reached after a careful review of all the evidence available. Submitted as a table of recommended daily allowances for specific nutrients (see page 335), they call for protein of a type found best in dairy products and in meat or fish, for calcium, for iron and for several vitamins at specific levels for varying age and activity. While cereals occupy an important place in food economy, to meet these higher standards of nutritional economy more liberal allowances of dairy products, meat, fish, fruits and green or yellow vegetables than formerly were considered necessary will be demanded.

Sir John Orr, scientific adviser on nutrition to the war cabinet in Britain, expressed the opinion that the "Washington nutrition yardstick," as he termed the table of recommended daily allowances of specific nutrients, should receive official recognition in England and serve there as well as here as a guide in planning for nutrition. This table, which is reproduced on page 335 of this book, probably will also serve—it ought to serve

1b. The reader is urged to see an excellent discussion by Graubard of the influence of taboos on the diets of primitive and modern population groups: "In his quest for food primitive man showed amazing inventiveness and ingenuity. . . . In the absence of vitamin knowledge he usually succeeded quite unconsciously . . . to satisfy all protective requirements. That he is not urged to do so by an inner drive, as are many animals, is quite clear from the number of cases where he goes wrong. But that he succeeds at all, on an exclusive meat, milk or vegetable diet with often fantastic prohibitions and regulations is indeed a wonder." (Graubard, Mark: *Food Habbits of Primitive Man*, Scientific Monthly, October-November, 1942, pp. 342-348, 453-460.)

—to guide what plans are made for feeding people everywhere. In that case the demand for milk, meat, fruits and other rich sources of the nutrients called for by the "yardstick" will tax resources to the limit. This raises questions whether foods now commonly available are used as economically as possible and whether foods not commonly in use but equally, or even more, nutritious could serve as supplements to common foods.

DAIRY PRODUCTS

Milk tops all lists of foods of high nutritious qualities, but wasteful practice enormously restricts its use for human food. Much milk is separated. The cream is used for making butter, and what is left is fed to animals or discarded. Until quite recently, only 12 per cent of the skim milk produced in the United States was used for human food. Objection to skim milk is mainly due to prejudice and is based on the erroneous conception that skimming removes the major value of the milk. A market for dried skim milk is growing among commercial manufacturers of bread and several other processed foods, but a public demand for such a product has not existed. In the United States some sixty billion pounds of skim milk is produced annually,² but around fifty billion pounds remains on the farms and is fed to calves, pigs and poultry. This will continue to be the situation until the farmer can obtain sufficient returns for skim milk to induce him to deliver the whole milk to the creamery or to substitute other protein feeds for skim milk in his feeding operations. Skim milk fed to farm livestock and poultry eventually reaches the human stomach in the form of meat and eggs, but it would make a greater contribution to the nutrition of our people if it were consumed as skim milk. The nutrients in skim milk, pound for pound, equal those of muscle meat, and it appears that 10 pounds (4.5 Kg.) of the nutrients of skim milk is required to produce 1 pound (0.5 Kg.) of food nutrients in the form of pork.³

The quart of liquid milk a day for children and the pint for adults, as recommended in much nutrition teaching, is more than many family budgets will allow; but why insist on liquid milk? Milk can be distributed

2. Consumer's Guide, U. S. Department of Agriculture, July 1939.

3. Abbott, J. S.: The Food Value and Economics of Skim Milk. *Am. J. Pub. Health* 80: 237-239 (March) 1940.

for much less cost as dried whole milk, and dried skim milk, which is relatively little perishable, can be sold for much less than the cost of liquid whole milk. The fats of milk, except for a content of vitamin A, are not superior to other less expensive fats, and vitamin A can be found in much less costly foods than milk.

Most diets not providing milk afford less calcium and less riboflavin than are called for by the recommendations of the Food and Nutrition Board, yet many persons dislike milk and never drink it. A great advantage of dry skim milk is that it can be mixed with other foods in cooking, so that the consumer gets it painlessly. Indeed, much more milk solids can be put in bread, cakes and puddings by using dry milk powder than when liquid milk is used. The water in liquid milk limits the amount that can be added. The taste of reconstituted dry milk is less attractive than that of liquid milk, but the taste of custards and other cooked foods made with dry milk differs not at all from, or is superior to, the taste of similar products made with liquid milk. Buttermilk is also highly nutritious, matching skim milk in its content of vitamins and minerals.⁴ It also can be dried and thus distributed more economically.

The delicious taste of butter assures its marketing. However, to produce milk, as has been the custom, only for its butterfat has no advantage from the standpoint of nutrition and is grossly unsound economically, even for the producer.

Cheese mostly represents the casein in milk.⁵ Superb as a food because of the high biologic value of its protein and because of its content of calcium, cheese could be more largely used with great advantage. Most persons like it, but city dwellers take too little of it. The European peasant makes much more of cheese. It represents a substantial portion of his diet, and large consumption of cheese undoubtedly contributes to the proverbial vigor of the pastoral peoples of Asia and the Balkans.

Left over from the milk when cheese is made is whey. The water of the milk is in the whey, but with it part

4. Hutchison, Robert: *Hutchison's Food and the Principles of Dietetics* (Revised by V. H. Mottram and George Graham), ed. 9, Baltimore, Williams & Wilkins Company, 1940.

5. McCammon, R. B., and Kramer, M. M.: Nutritive Value of Various Types of Cheese, *J. Am. Dietet. A.* 9: 292-294 (Nov.) 1933,

of the protein—the lactalbumin—some of the mineral matter and most of the vitamins, yet whey is mostly thrown away by manufacturers of cheese. In late years dried powdered whey has found a place in poultry feeds and in candy manufacture. Much more dried whey could be used for human food, and none should be discarded. It is reported that in Germany no milk products may be thrown away and none may be used for feed without a special license.

Sugar is not among the recommended foods. Its recent rationing will not provoke a hardship, for sugar supplies nothing in nutrition but calories, and the vitamins provided by other foods are sapped by sugar to liberate these calories. One of the worst of the many bad food habits that Americans have acquired is their use of sweetened carbonated beverages. Many persons take such beverages by the half pint many times a day, with a resulting excessive consumption of sugar. The suggestion has been made⁶ that whey after removing its protein be incorporated in these beverages. By such means the minerals and vitamins of whey could make these drinks nutritious.

MEATS AND FISH

Next to the dairy products on the list of better foods come meat and fish, but in their use economy has been neglected. There is no evidence that the nutritive value of muscle meat differs significantly from one part of the animal to the other, yet small food budgets are regularly taxed by purchases of expensive cuts when thrifty cuts would do as well.⁷ Furthermore, the most nutritious parts of every carcass are seldom chosen by the customer and go to making fertilizer or feed. The blood, lungs, stomach, liver, pancreas, kidney, brain and heart are spurned by many persons. In southern China a suitable gift for a prospective mother is a pair of pig's feet. She will hope by the time the baby is born to have accumulated perhaps two dozen pairs to help support her demand for calcium during lactation.⁸

6. Wilder, R. M.: Nutrition in the United States: A Program for the Present Emergency and the Future, *Ann. Int. Med.* **14**: 2189-2198 (June) 1941.

7. A useful pamphlet is that issued by the American Meat Institute, Chicago, entitled "Buying Guide for the Thriftier Cuts of Meat." The statements in the pamphlet were approved by the Council on Foods and Nutrition of the American Medical Association.

8. Rose, Mary S.: Racial Food Habits in Relation to Health, *Scient. Monthly* **44**: 257-267 (March) 1937.

In the first world war the complaint was made by Reese⁹ that Americans had acquired "a lot of silly ideas" about what is fit for food and what is not. Thereupon Reese advocated the use of certain reptiles, such as turtles, lizards, snakes and even alligators. A happy habit of more primitive man was to devour whatever could be eaten in the carcass of his kill. He thus obtained the organ meats as well as muscle. The Navajo, for example, who in contrast to many other Indian groups has retained his vigor despite proximity to the white man's civilization, consumes all vestige of the sheep or goat he kills and exhibits a decided preference for the contents of the abdomen.¹⁰ He eats the organs first. The modern American credits the ancient Greeks with a high state of culture, yet Cornwall¹¹ found references in the *Odyssey* to many foods men spurn today—foods such as roasted entrails and goat's stomach filled with blood. There is current discussion of deficiency of certain lipoids in the diet of more civilized races. A return to these food habits of the ancient Greek and modern Navajo would at once correct such dietetic error, for the lipoid content of organ meats such as liver is high. Much could be done to improve the nutritive quality of processed meats by including in them organ meat and blood. Blood sausage (*blutwurst*) is popular in Germany. The dog food manufactured by American packers, containing much of what they designate as offals, is demonstrably superior in nutritive value to most of the meat they can for human food.

The nutritive values of fish are as high as those of meat, except perhaps for iron.¹² The livers of many fish besides the cod are rich in vitamins A and D; also the body oils of fish contain these vitamins. The flesh of fish is also rich in vitamins of the B groups to such an extent that Goldberger and Wheeler¹³ found salmon to be effective for preventing pellagra. However, many fish equal in nutritive value to fish that are

9. Reese, A. M.: *Reptiles as Food*, *Scient. Monthly* 5: 545-550 (Dec.) 1917.

10. Carpenter, T. M., and Steggerda, Morris: *The Food of the Present Day Navajo Indians of New Mexico and Arizona*, *J. Nutrition* 18: 297-305 (Sept.) 1939.

11. Cornwall, E. E.: *What the Ancient Greeks Ate*, *Ann. M. Hist.* 9: 30-33 (Jan.) 1937.

12. Sherman, W. C.; Elvehjem, C. A., and Hart, E. B.: *Further Studies on the Availability of Iron in Biological Material*, *J. Biol. Chem.* 107: 383-394 (Nov.) 1934.

13. Goldberger, Joseph, and Wheeler, G. A.: *A Study of the Pellagra Preventive Action of Canned Salmon*, *Pub. Health Rep.* 44: 2769-2771 (Nov. 15) 1929.

popular in American markets are neglected, notably the carp. Smoked carp is a delicacy in Europe, and carp culture in Germany is an industry of importance. Raising carp is said to be as profitable as raising pigs. American streams and fresh water lakes are full of rough fish which could be utilized for human food.

The huge oyster shell mounds of the Atlantic coast seem to testify that the aboriginal American made more use of oysters than happens now. A nutritional advantage in the oyster, which applies also to the clam, the lobster, the crab and the shrimp, is that it is eaten whole, so that the valuable nutrients of the internal organs are obtained. Pease¹⁴ maintained that the nutritive value of oyster meats is a little higher than that of cow's milk, owing to a high content of calcium, iron and other minerals and all the vitamins.

Fairchild,¹⁵ on a tour of the world, found giant snails as large as a man's fist offered for sale in Ceylon and Africa. They were considered a delicacy. He thought they might be raised in the Everglades of Florida for consumption in America.

For mention also without prejudice is the possibility of finding protein foods among the insects. Wakefield and Dellinger,¹⁶ in the feces of pre-Columbian bluff dwellers of the Ozarks, found residues of insects. A modern primitive, the Bushman, considers appetizing the eggs of termites.¹⁷ Verrill¹⁸ has written that the grasshopper and the cricket were periodically important as foods for the Indians of the western plains, and in the West Indies a large white grub found in the pith of palm trees serves as food. These grubs when toasted are said to taste like roasted chestnuts. Even the ancient Hebrews, strict as they were in their choice of foods, looked with favor in times of famine on the locust.¹⁹ The nutritive value of insects must be high.

14. Pease, H. D.: *The Oyster—Modern Science Comes to the Support of an Ancient Food*, J. Chem. Educ. 9: 1675-1712 (Oct.) 1932.

15. Fairchild, David: *Exploring for Plants*, New York, Macmillan Company, 1930.

16. Wakefield, E. G., and Dellinger, S. C.: *Diet of the Bluff Dwellers of the Ozark Mountains and Its Skeletal Effects*, Ann. Int. Med. 9: 1412-1418 (April) 1936.

17. Altschuler, S. S.: *The Historical and Biological Evolution of Human Diet*, Am. J. Digest. Dis. 1: 215-218 (May) 1934.

18. Verrill, A. H.: *Foods America Gave the World*, Boston, L. C. Page & Co., 1937.

19. Dor: *Explication zoologique des prescriptions alimentaires de la Bible et du Halmud*, Bull. et mém. Soc. d'anthrop. de Paris, series 8, 8: 63-70, 1937.

The taste may not be bad. Insect culture might some day become a part of food economy.

Should the time ever come when the land fails to provide enough good protein to meet all human needs, an unlimited supply can be found in the sea. The catch of fish has limitations, but ubiquitous in the oceans is the zooplankton, which could be harvested and would provide a first class human food. However, the technical difficulties involved are rather overwhelming. The estimate has been made by Clarke²⁰ that the human requirement for calories for one individual could be met only by all the plankton in a volume of water "equal to a football field filled to a depth of a meter and a half."

More practical than plankton as a source of proteins is the micro-organism yeast. A by-product now and mostly thrown away by brewers, yeast could be grown in limitless amounts. Dried yeast is largely protein, 40 to 55 per cent. Most of the nitrogen free remainder is material consisting of a mannose polysaccharide. The amount of fat is small, from 1 to 3.5 per cent, but this is rich in steroids. The content of vitamins of the B complex is very high; some vitamin A is present and much ergosterol, which by ultraviolet irradiation could be changed to vitamin D. This is important because almost no foods other than fish liver oils provide significant amounts of vitamin D. Among the amino acids found in the proteins of yeast are alanine, valine, phenylalanine, glutamic acid, aminoacetic acid, leucine, oxyproline, aspartic acid, cystine, methionine, tyrosine, proline and tryptophan. The percentage of these ranges from 10 down to 0.5 in the order given. The diamino acids present include lysine 10 per cent, arginine 5 per cent and histidine 5 per cent.²¹

Some brewers' yeast is on the market now, sold mainly as a source of vitamins. The armed forces are receiving yeast in peanut butter as an optional spread for bread. The yeast taste is disguised by that of the peanut. Analysis of samples of such yeasted peanut butter (20 per cent) indicates a composition of approximately 32 per cent protein. The samples contain per gram around 30 micrograms of thiamine, 16 micro-

20. Clarke, G. L.: Plankton as a Food Source for Man, *Science* **89**: 602-603 (June 30) 1939.

21. Anheuser-Busch, Inc.: Personal communication to the authors.

grams of riboflavine and 250 micrograms of nicotinic acid. Thus an ounce (30 Gm.) of such peanut butter should provide about 10 Gm. of valuable protein, about half the recommended daily allowances of thiamine and nicotinic acid and a fifth of the recommended daily allowances of riboflavin.²¹

Two products, mixtures of vegetables and brewers' yeast, are listed in Accepted Foods.²² Bakers' yeast also has virtue as a food for persons who can eat it without abdominal distress. It is much less rich in thiamine than brewers' yeast; also some question remains as to the utilization by man of the vitamin B complex in fresh yeast.^{22a} A high thiamine bakers' yeast has recently been made available to fortify the dough of enriched bread.

The bitter taste of yeast and some aftertaste present complications to the use of yeast as food, but these objectionable qualities can be overcome. Some special yeasts have very little bitterness, and autolyzing yeast provides a product with a taste like meat. The possibilities of yeast as human food deserves more technological attention. Two major defects in many modern diets are relatively small provision of certain vitamins of the B complex and insufficiency of biologically superior protein. Both deficiencies could be limited by using yeast as food.

FRUITS

Another basic nutrient deficient in many diets is ascorbic acid, vitamin C. The trouble mainly comes from lack of fruit in diets, especially lack of citrus fruits. The tomato is good as a source of ascorbic acid, but many fruits such as apples and pears, most of the vegetables, milk and meat are far from rich as sources of this vitamin. However, citrus fruits and tomatoes, while grown abundantly in certain sections, are bulky, perishable commodities and hence expensive to distribute. Ascorbic acid can be made synthetically at relatively small expense, and it may prove to be desirable to add the synthetic vitamin to jellies, jams

22. American Medical Association Council on Foods: Accepted Foods and Their Nutritional Significance, Chicago, American Medical Association, 1939.

22a. Parsons, Helen, and others: Utilization by Man of the Vitamin B Complex in Fresh Yeast, Federation Proceedings, vol. I, part II, p. 129, March 16, 1942.

and other fruit preserves in such amounts as to bring the final content of ascorbic acid to that of ripe tomatoes.

Among less common foods which are rich in ascorbic acid is the black currant. Two ounces of black currants, cooked, according to Olliver,²³ will meet an individual's vitamin C requirements. The reference probably applies to minimal requirements. Consumed raw, watercress and strawberries are good sources of ascorbic acid, providing approximately 60 mg. per hundred grams. The edible hips of the wild rose are becoming famous for their content of this vitamin.²⁴ Thone²⁵ has suggested that the hip could be increased in size and developed commercially. Verrill,¹⁸ whose thesis is that North Americans should use more foods from South America, mentioned some of the unusual tropical fruits now on sale at a few exclusive markets in this country. They include the mamey, sapodilla, silkana, ceriman, papaya, anona, soursop, star apple and guava. Papaya has recently been suggested as a substitute for orange in Hawaii, as well as home made guava juice.^{25a} Guava has an especially high content of ascorbic acid. Goldberg and Levy²⁶ found 300 to 400 mg. in each hundred grams of the fresh fruit, and on drying the guava fruit they obtained a powder of pleasant aromatic odor and practically no taste, with the rather phenomenal quantity of 2,500 to 3,000 mg. of ascorbic acid for each hundred grams. A monograph on the guava is now in preparation by Webber of the California Agriculture Experiment Station.²⁷

VEGETABLES

An important reason for the great amount of emphasis that nutritionists have placed on green and yellow vegetables is the content of beta-carotene in spinach, carrots, beet greens and other colored plants and roots. There is widespread misconception to the effect that chlorophyll has a place in animal nutrition. There is

23. Olliver, Mamie: Antiscorbutic Values of Fruits and Vegetables, *Lancet* 2: 190-192 (Aug. 17) 1940.

24. Loewenfeld, Claire: Vitamin C from Rose Hips, *Brit. M. J.* 1: 988-989 (June 21) 1941.

25. Thone, Frank: Wealth from Weeds, *Science News Letter* 40: 166-167 (Sept. 13) 1941.

25a. The Child, *Monthly Bull. U. S. Dept. Labor, Children's Bureau*, May, 1942, p. 292.

26. Goldberg, Leon, and Levy, Leopold: Vitamin C Content of Fresh, Canned and Dried Guavas, *Nature, London* 148: 286 (Sept. 6) 1941.

27. Webber, H. J.: Personal communication to the authors.

no evidence to support such a view.^{27a} Carotene alone and not the chlorophyll of plants is converted in the animal organism to vitamin A. Few foods provide vitamin A ready made. Butter and fish liver oils are about the only sources. Butter may be excellent as a source or only fair, depending on the feed supplied the cow. Assays run from less than 2,000 to more than 40,000 international units to the pound. The daily allowance of vitamin A for an adult man, as recommended by the Food and Nutrition Board of the National Research Council, is 5,000 units, and one of the greatest services the dairy industry could perform would be to standardize the vitamin A content of butter at some high level.

Interference with the fisheries of the world by the war has again directed attention to sources of carotene. Plant oils contain no preformed vitamin A and but little carotene.^{27b} However, the pulp of certain yellow vegetables is very rich in carotene. An estimate by Barnett²⁸ suggests that 10,000 acres planted in carrots would yield 20 trillion units annually of vitamin A. This would amount of 4 billion daily human requirements, or enough to last a population of 100 million persons forty days. Another good source of carotene is the sweet potato, a prolific grower.

Many vegetables little known in North America deserve attention by the food economist. Some could be developed with advantage. The taro, for example, has a subterranean stem resembling the potato. The yield per acre is two to four times that of the potato and, measured in calories, may be ten times that of rice.²⁹ Taro is a common food in mid-Pacific islands, in parts of southern Asia and in South America. Varieties known as dasheens have been cultivated commercially in parts of the United States.³⁰ Taro in Hawaii is mostly eaten as a paste called poi. Fermented poi keeps well without refrigeration. Another

27a. Kohler, G. O.; Elvehjem, C. A., and Hart, E. B.: The Relation of Pyrrole-Containing Pigments to Hemoglobin Synthesis, *J. Biol. Chem.* **128**: 501-509 (May) 1939.

27b. The oil of the red palm is said to provide the natives of tropical West Africa with vitamin A. (A. L. Bacharach, personal communication.)

28. Barnett, H. M.: Plenty of Vitamin A Is Available for the United States, *Science News Letter* **40**: 85 (Aug. 9) 1941.

29. Potgieter, Martha: Taro (*Colocasia esculenta*) as a Food, *J. Am. Dietet. A.* **10**: 536-540 (June-July) 1940.

30. Young, R. A.: The Dasheen: A Southern Root Crop for Home Use and Market, U. S. Department of Agriculture, Farmer's Bull., June 1924, No. 1396.

vegetable of the tropics said to be high in nutrients is the breadfruit.³¹ Others are yautias or taniens, which serve importantly as food for the natives of the West Indies, and yuca, the edible root of the cassava plant, the source of tapioca. Widely used for food today in South America, as mentioned by Verrill,¹⁸ and cultivated by the Incas of Peru before the white man came, are the canna, the leren, the arikuna, the papa lisa, the oca and the arracha, as well as the better known peanut, the potato and the sweet potato.

Use of grass for human food again has come up for consideration since the present war began. Nebuchadnezzar was compelled to "eat grass as oxen" to atone for many sins. However, the benefit he derived, if any, was largely spiritual. The value of a food, as emphasized by Graham Lusk³² before World War I, depends mainly on the ratio of nutritive to non-nutritive components. Due consideration must be paid to a few special requirements, such as that for vitamin C. The citrus fruits and tomatoes, for example, although bulky, are of great importance in nutrition because of their content of ascorbic acid. Lusk once missed this point, as he later acknowledged.³³ He called tomatoes colored water, but by and large his early emphasis was right. The more nutritious foods are those with nutritive components high and non-nutritive components—namely, water and indigestible cellulose—low. Among the vegetables the tubers like potatoes and the legumes like peas and beans possess more of this quality than do the leaves of plants or grasses.

In times of famine, however, people will resort to whatever they can find to eat. In Russia, for example, in the last war not only grass but also the leaves and the bark of trees were eaten. In Germany and Russia enormous amounts of watery root vegetables, such as turnips, were consumed. In a population leaning too heavily on such foods, war edema is likely to develop. The type of protein obtained is poor and excessive water is ingested. Also the bulk of watery foods which needs to be ingested to contribute significantly to caloric

31. Vaughan, W. T.: An Introduction to Tropical Foods, *J. Am. Dietet. A.* **16**: 110-116 (Feb.) 1940.

32. Lusk, Graham: *The Fundamental Basis of Nutrition*, New Haven, Yale University Press, 1914, p. 42.

33. Lusk, Graham: *Problems of Metabolism*, in *Lectures on Nutrition*, Philadelphia, W. B. Saunders Company, 1924-1925, p. 62.

requirements places an intolerable strain on the human intestine. The coarseness and amount of fiber some such foods contain may even interfere with absorption of what nutrients are present. The Germans as well as the Russians in the last war attempted to eke out dwindling supplies of flour by adding to this flour bran and chaff and even straw. By doing so they made bad matters worse. Nutrients diluted with large amounts of indigestible material are lost; they cannot be absorbed effectively.

Thus grass serves poorly as a human food. Even tender, leafy vegetables, valuable as a source of minerals and carotene, would not alone provide for human nourishment. Their protein would be inadequate and their water content excessive. However, all the leafy vegetables have a place as supplements to other foods, and tender young grass when dehydrated is excellent as a vehicle for several vitamins and salts. Such a product has been accepted by the Council.³⁴

THE CEREAL GRAINS AND THE LEGUMES

Relative ease and low cost of production and high content of energy yielding nutrients explain why cereal grains, rice and also corn have long contributed importantly to the diets of people whose civilizations have been based on agriculture. Wheat has been developed more than other grains. In England a hundred years ago wheat alone contributed nearly half of all the calories of the diet. Its consumption has been halved, and yet today it provides more calories for the English speaking world than any other food.

Oat consumption could be encouraged with considerable advantage. Oats can grow much farther north than wheat, and oats provide a somewhat more nutritious human food. The content of thiamine is higher and the protein is biologically superior. This explains the value of oats as feed for stock. Samuel Johnson's caustic commentary in his Dictionary that "oats in England is generally given to horses and in Scotland supports the people" illustrates how prejudice works hardships in nutrition. In England, then as now, just as in America, men were more concerned about good nutrition for their livestock than for themselves. The answer said to have been given to Samuel Johnson was

34. *Cereal Grasses in Special and Therapeutic Diets*, Kansas City, Missouri, Cerophyl Laboratories, Inc., 1940.

"and where will you see such horses and such men." The Scots became a hardy race on oats. So did the early Norse. Oatmeal is often mentioned in the Sagas.³⁵

Rye and barley are less popular than wheat in England and America. They are much more used in Europe. Rye is not superior to wheat in nutritive qualities, and rye flour, like white wheat flour, is generally overmilled. Also what there is of rye in most so-called rye bread is usually diluted with white wheat flour.

Decortication of the grains by modern milling methods has been unfortunate from the standpoint of nutrition. The stone mills of the past left in the flour a large proportion of its vitamins. The flour was coarse and not very white, but in content of thiamine and nicotinic acid it far surpassed the finer flour of the roller mills. The latter came into general use some seventy years ago. The adequacy in certain vitamins, notably thiamine, of the diet of the populations of England and America—the adequacy especially of the diet of that part of the population of these countries which because of smaller purchasing power consumes much bread—was largely affected in consequence of technology applied to milling grains without the benefit of direction by a science of nutrition. There was no such science when these modern milling methods started.

The effect of roller milling on the thiamine content of American diets has not been estimated. Presumably, however, it was much the same as that in England. Drummond's³⁶ calculation of the nutrients contained in diets past and present is shown in accompanying table. The comparison reveals that the diet of the middle class Englishman in recent years, while supplying more vitamin A and more ascorbic acid, contains little more than a third as much thiamine as did the diets of the past. In other respects the differences are less significant. The greater use of green vegetables and fruits in recent times accounts for the increased supply of the vitamins A and C. The substitution, about 1870, of roller milled white flour for the coarser flour of the past and the

35. Gudjonsson, S. V.: *Kost der alten nordischen Völker*, Deutsche med. Wchnschr. 61: 1507-1510 (Sept. 20) 1935.

36. Drummond, J. C., and Wilbraham, A.: *The Englishman's Food: A History of Five Centuries of English Diet*, London, J. Cape, 1940.

increased use of sugar explain the smaller allowances of thiamine in the modern diet. The milling industry of the United States is thoroughly aware at last of the importance of retaining in flour more of the thiamine and nicotinic acid of wheat. This ultimately will be accomplished without loss of other qualities which people have come to like and to demand in flour. Until it is accomplished, which may take many years and involve perhaps a revolution in the milling industry, restorative additions of thiamine and nicotinic acid to

Analysis of English Diets for Adult Men

	Calo- ries	Pro- tein, Gm	Cal- cium, Gm	Iron, Mg	Vitamin A, Inter- national Units	As- corbic Acid, Mg.	Thia- mine, Mg.
Middle class diet today..	3,310	110	0.6	12.3	5,170	70	1.2
Poverty diet today....	3,000	78	0.3	8.4	520	15	0.66*
Middle (artisan) class diet, 1826... ..	2,130	125	0.2	45	1,220	0	1.77
Navy ration, 1811.....	2,750	110	0.7	18	2,600	0	3.15
St. Bartholomew's Hos- pital, 1686	2,600	80	1.9	12	5,100	10	1.89
Meat eating classes, fif- teenth century.....	3,650	250	1.3	50	7,000	?	3.30
Peasant diet, fifteenth century.....	3,300	140	1.2	21	1,700	10-20	4.20
Recommended by Food and Nutrition Board †	3,000	70	0.8	12	5,000	75	1.8

From J. C. Drummond's "The Englishman's Food," London, J. Cape, 1940.

* A diet containing as little thiamine as this (0.22 mg. per thousand calories) provokes symptoms of severe athlaminosis. See Williams, R. D.; Mason, H. L.; Smith, B. F., and Wilder, R. M.: Further Observations on Induced Thiamine (Vitamin B₁) Deficiency and the Thiamine Requirement of Man, Arch. Int. Med. 69: 721-738 (May) 1942.

† For moderate activity.

white flour and bread should be demanded. Restoration to staples such as flour of nutrients removed in processing was recommended in 1939 by the Council on Foods and Nutrition of the American Medical Association.³⁷ The procedure as applied to flour and bread was later endorsed by the Food and Nutrition Board of the National Research Council. Flour now is standardized and controlled by the Food and Drug Administration. White flour which bears the label "enriched" must contain thiamine and nicotinic acid, as well as

37. Annual Meeting of the Council on Foods, J. A. M. A. 113: 680 (Aug. 19) 1939.

iron, in amounts which are believed to approximate those in flour as flour was milled a century ago.^{37a}

The nutritional environment of enormous populations of the Orient, which largely depend on rice for food, also suffered badly from food technology applied without the benefit of science. Milling rice is much like milling wheat. The primitive milling methods removed the husks but left brown rice with much of the bran intact. The later milling methods removed the bran coats and with them much of the content of vitamins and salts. The later methods yielded so-called polished rice. An example of how misguided man can be was supplied by Hou,³⁸ who wrote that in the rice country of China where beriberi is endemic the quite nutritious soybean is used for field fertilization in the cultivation of the less nutritious rice. One can buy brown rice in American markets, but only at a premium. It spoils and hence its distribution costs are high. A better buy is what is called unpolished rice. Unpolished rice is said to retain about a half of the thiamine of brown rice. It keeps well and after cooking is almost as white as polished rice.

Food habits to a great extent depend on the availability of foods. The story of the pottage of lentils for which Esau, son of Isaac, sold his birthright to his brother Jacob suggests that lentils were more used in ancient times than now. In Germany lentil soup is still in favor, yet in nearby Belgium lentils, which were distributed in World War I, were spurned by people who were starving. There is no disputing the nutri-

37a. The idea that the nutrient quality of flour can be adequately corrected by retention of the wheat germ is fallacious. While the germ is rich in vitamins and other important nutrients, its contribution to the weight of the grain of wheat is so small—less than 2 per cent—that retaining it in milling insignificantly affects the total content of vitamin in the flour. Furthermore, it would not contribute to the flour problem as a whole to take the wheat germ from some wheat to fortify flour from other wheat, assuming that at some later time methods of milling will be developed that permit the manufacture of a white flour containing all the vitamins of the wheat. However, a large amount of corn germ is available from the corn used by the distilleries, and we are informed (personal communication from VioBin Corporation, Monticello, Ill., Oct. 28, 1942) that if a demand were created for corn germ sufficient to "make it pay to take it out they (the distilleries) would be happy to do it." Corn germ, like wheat germ, is rich in protein of high nutrient quality and excellent as a source of factors of the vitamin B complex. Failure to use corn and wheat germ that could be derived from commercial uses of corn and wheat other than making flour is one more example of a valuable food that now is wasted.

38. Hou, H. C.: *Diet and Health in China*, Chinese M. J. 53: 413-420 (Sept.) 1937.

tional excellence of lentils. Likewise meritorious as foods are peanuts and soybeans.³⁹ The proteins of these legumes are biologically complete, superior to those of any of the cereals. The vitamins of the B complex and minerals are abundant. The Japanese eat boiled or roasted soybeans from bags like candy.⁴⁰ A popular food in Hawaii is miso, a fermented mixture of soybean and rice. The soybean is a staple in certain parts of China, and the statement frequently is made that in these regions beriberi and pellagra are unknown. In Germany, cultivation of the soybean and its processing for human food has become a major industry. A sausage known as bratling, made with skim milk and soybean, forms a mainstay of the German army ration.⁴¹ In the United States the press cake that remains after expulsion of the oil from soybean, peanut or cottonseed is sold for feed or is discarded. The industries get their profit from this "premium oil," which in part is used for food, in part for other purposes. Yet the press cake contains nutrients which are almost, if not quite, as valuable as the nutrients of meat and can inexpensively be converted into soups and other very tasty foods. The cost of production of protein from soybean plants is little greater than a tenth the cost of production of meat protein, and the present relatively small annual crop of peanuts and soybeans in the United States would provide 70 per cent as much protein as does the meat supply.

CONCLUDING COMMENT

This very brief review will show that modern man could reconsider many of his food ways with immeasurable advantage. Greater and more economical use of milk and meat and the use of more organ meat and fish would help to raise the quality of diets. Some common foods can be improved and greater use of many uncommon foods would help provide more adequate nutrition. The world is full of food potentialities, and the anticipated demands for foods possessing superior nutritive qualities calls for a reevaluation of world supplies of

39. Horvath, A. A.: *The Nutritional Value of Soybeans*, Am. J. Digest. Dis. 5: 177-183 (May) 1938.

40. Miller, C. D.: *Japanese Foods Commonly Used in Hawaii*, Hawaii Agricultural Experimental Station Bull., 1933, vol. 68.

41. *The Soya Bean*, editorial, Brit. M. J. 2: 269-270 (Aug. 23) 1941.

food. The reevaluation, if based on the science of nutrition, should reveal the means of providing all that is required for the optimal nutrition of all the populations of the globe, which well may be prerequisite for world security and order.

CHAPTER XV

THE PRESERVATION OF THE NUTRITIVE VALUE OF FOODS IN PROCESSING

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The prodigious increase in the consumption of succulent vegetables and fruits makes an interesting statistical study. A century ago most of the people of the United States regarded tomatoes as poisonous, and when children ate them inadvertently medication to counteract their "toxin" was not unusual. In 1918 Hess¹ recommended tomato juice as an antiscorbutic for 3 month old infants, and in later publications he stated that infants can tolerate twice as much tomato juice as orange juice. Today tomato juice is the leader in volume of an array of ever available fruit juices. Many a middle aged person who takes for breakfast a glass of orange juice comprising two or three normal size fruits can well remember when one such fruit in his Christmas stocking was his annual quota. Samuel Pepys once drank a whole glass of orange juice and was surprised that he did not become ill.

Less phenomenal growths have occurred in the consumption of all succulent vegetables, but their wide distribution has eliminated seasonal and regional effects. How vegetables fit into present day nutritional aims has recently been pointed out in *THE JOURNAL*:² The average thiamine and riboflavin contents of a large number of vegetables are, respectively, 2.8 and 2.4 mg. per thousand calories, whereas the amounts added to enrich flour are 1 and 0.7 mg. respectively per thousand calories.

Even ancient man must have observed that certain root vegetables, such as parsnips, retain their edible qualities in the earth during extreme cold, while others, such as carrots, can stand only more moderate freezing

1. Hess, A. F., and Unger, L. J.: Canned Tomatoes as an Antiscorbutic, *Proc. Soc. Exper. Biol. & Med.* **16**:1-2 (Oct. 16) 1918.

2. Kohman, E. F.: Comparative Food Sources of Thiamine, *J. A. M. A.* **117**:881 (Sept. 6) 1941.

and some are damaged by mild freezing. As a result, the vegetable pit was evolved as the most primitive method of processing succulent foods for their preservation, now exemplified in refrigeration under controlled temperature, humidity and atmospheric gases, and the recent modification designated "frosted" or "frozen foods."

Evidence that our vitamin age cannot lay claim to the first realization of the importance of the succulent and perishable foods in our nutrition is the evolution of the art of canning stimulated by the requirements of Napoleon's armies.

Paradoxical as it sounds, lack of heat (refrigeration) and application of heat (canning) have come to be the two major means of preserving perishable foods for use at all times and places. Today investigators are evaluating the efficacy of these in preserving essential nutrients, emphasizing, as has recently developed knowledge on nutrition, the vitamins. A short review of the many experiments conducted on this point can only touch on the most pertinent, but these make it possible by inference and analogy to draw certain general conclusions.

EFFECT OF STORAGE AND COOKING ON VITAMIN C

Among the fruits, apples are prominent in lending themselves to cold storage. Recently, Eheart³ reported an average loss of 20 per cent of the vitamin C content during twelve weeks in experiments involving sixteen varieties of apples, two seasons and temperatures ranging from 35.3 to 37.9 F. A loss of one third occurred in from eighteen to twenty-four weeks. Other investigators have reported lower losses at 32 F., the practical minimum for apple storage. In cooking apples Eheart encountered losses which could be ameliorated by previously keeping the peeled and cored apples submerged in a 2.5 per cent salt solution for twenty-four hours, the sodium chloride serving to keep the apples from darkening. The losses of vitamin C with three methods of cooking apples submerged and apples not submerged in salt solution are recorded in table 1. Kohman and

3. Eheart, Mary S.: *Factors Which Affect the Vitamin C Content of Apples*, Virginia Agric. Exper. Sta., technical bulletin 69, March 1941. pp. 1-16.

Sanborn ⁴ showed in 1924 that in commercial canning apples submerged for sixteen hours at room temperature consumed all the oxygen within their tissues. This pretreatment is now accomplished in an hour at 120 F. Apples so treated may be canned without measurable loss of vitamin C and after a few months storage are more potent in this factor than similar apples stored under refrigeration.⁵

These experiments indicate that oxygen may play a distinctly destructive role toward vitamin C. They indicate but do not prove that heating is without effect. This was shown by increasing the normal processing of canned peas from twenty-five minutes to fifty minutes at 250 F.⁶ without there being any increased destruction of vitamin C. Many foods have reducing effects on oxidized (dehydro) ascorbic acid, as was strikingly demonstrated in peas ⁷ and as the following unpublished

TABLE 1.—*Losses of Vitamin C from Apples*

Method of Cooking	Previously Submerged, per Cent	Not Submerged, per Cent
Apple sauce.....	58	91
Fried apples.....	68	80
Apple pie.....	91	92

experiment illustrative of a common behavior of many foods shows: Tomato juice was extracted without incorporating air and the ascorbic acid determined with 2,6-dichlorophenolindophenol. The juice was then divided into two portions, to one of which dehydro ascorbic acid was added. This did not affect the titration value. All the air was evacuated from both portions in pyrex glass flasks, which were sealed and heated for thirty minutes under boiling water. The titration value of the portion to which oxidized ascorbic acid had been added on cooling was 7.5 per cent higher than previously, whereas the other was unchanged. The fact that heating a food in itself need not be destructive of vitamin C must be

4. Kohman, E. F., and Sanborn, N. H.: The Nature of Corrosion in Canned Fruits, *Indust. & Engin. Chem.* **16**: 290 (March) 1924.

5. Kohman, E. F.; Eddy, W. H., and Carlson, Victoria: Vitamin C in Canned Foods: II. The Vitamin C Destructive Factor in Apples, *Indust. & Engin. Chem.* **16**: 1261 (Dec.) 1924.

6. Eddy, W. H.; Kohman, E. F., and Carlson, Victoria: Vitamins in Canned Foods: III. Peas, *Indust. & Engin. Chem.* **18**: 85-89 (Jan.) 1926.

7. Kohman, E. F., and Sanborn, N. H.: Vegetal Reduction of Dehydroascorbic Acid, *Indust. & Engin. Chem.* **29**: 1195 (Oct.) 1937.

kept in mind in considering the effect of cooking. Foods cannot be cooked without heat but they can be cooked in the absence of oxygen.

Floyd and Fraps⁸ have made practical application of avoiding oxidation of ascorbic acid in household cookery. In a large number of trials, rapid cooking of turnip greens, maintaining a constant rise of vapors to blanket off the atmospheric oxygen, resulted in only 15.5 to 26.7 per cent destruction of vitamin C, while slow cooking caused 23.8 to 36.5 per cent destruction. Covering the cooking vessel had no protective effect.

Storage losses of ascorbic acid may be greater in some products than in apples. Maine grown Green Mountain and Irish Cobbler potatoes⁹ in a month's storage at 15.5 C. lost 30 per cent ascorbic acid and in five months nearly 50 per cent. Lower storage temperatures for potatoes did not lower the losses. Loss in cooking becomes progressively greater with the following methods: steaming, boiling, baking and pressure cooking, but in no case did it exceed 25 per cent.

Clagett and Tottingham¹⁰ found that potatoes of several varieties grown in Wisconsin and stored for nine months at 4.5 C. were 20 per cent lower in ascorbic acid content than Triumph and White Rose potatoes recently shipped to Wisconsin markets from the Pacific coast.

Schuenert and Reschke¹¹ made a comprehensive study in Germany of storing and cooking potatoes. Steaming was found to result in the least loss of ascorbic acid. They assign to peeled, halved and steamed potatoes the following progressively smaller values with the advancing winter months: October, 18 mg. per hundred grams; November, 15 mg.; December, 13 mg.; January, 11 mg.; February, 10 mg.; March, 9 mg.; April, 8 mg., and May/June, 7 mg.

Cabbage¹² stored in a home vegetable cellar at about 45 F. and relative humidity of 55 for two months

8. Floyd, W. W., and Fraps, G. S.: Changes in Vitamin C Content During Boiling of Turnip Greens in Various Waters in Covered and Uncovered Containers, *Food Research* 5: 33-41 (Jan.-Feb.) 1940.

9. Rolf, Lydia A.: The Effect of Cooking and Storage on Ascorbic Acid Content of Potatoes, *J. Agric. Research* 61: 381 (Sept.) 1940.

10. Clagett, C. O., and Tottingham, W. E.: The Reducing Substance and Phenolic Compound Content of Potato Tubers in Relation to Discoloration After Cooking, *J. Agric. Research* 62: 349 (March) 1941.

11. Schuenert, A.; Reschke, J., and Kohlemann, E.: Ueber den Vitamin C-Gehalt der Kartoffeln, *Biochem. Ztschr.* 305: 1 (June) 1940.

12. Mayfield, Helen L., and Richardson, Jessie E.: The Effect of Winter Storage on the Vitamin C Content of Cabbage and Onions, *Montana State Bull.* 379, February 1940, pp. 1-12.

dropped from an original vitamin B₁ content of 45 Sherman-Chase units to 40, while after being cooked in generous amounts of water for ten minutes the unstored and stored fell respectively to 23 and 20 units. The vitamin C content in fall and spring was, in the raw state, respectively 63 and 47 mg. per hundred grams and after cooking 35 and 27 mg. Onions were found to change insignificantly.

Wellington and Tressler¹³ reported an actual loss of from 10 to 30 per cent of vitamin C in cooking cabbage by various methods, but the cooking water extracted as much as 66 per cent. With carrots¹⁴ loss of 14 per cent of their vitamin C was observed both when boiled and when steamed, but the vitamin C remaining after steaming was nearly all in the carrots, whereas the cooking water extracted vitamin C in proportion to the volume.

Parsnips¹⁵ containing in the fall from 12.8 to 39.9 mg. of ascorbic acid per hundred grams contained from 5.5 to 12.7 mg. after winter storage in the ground. Fall and spring parsnips boiled unpeeled contained respectively an average of 30.5 and 8.3 mg. of ascorbic acid per hundred grams, while boiled after peeling they contained respectively 15.3 and 7 mg.

Harris, Wissmann and Greenlie¹⁶ noted an average loss of 44 per cent in ascorbic acid in a number of vegetables at 41 F. with relative humidity of 65 per cent as against a 26 per cent loss with a relative humidity of 93 per cent. While vitamin A and thiamine losses were less, they too were better preserved at the higher humidity.

Fitzgerald and Fellers¹⁷ give the following average values, based on samples purchased weekly over a period of one year, for ascorbic acid in milligrams per

13. Wellington, Mary Elizabeth, and Tressler, D. K.: Vitamin C in Vegetables: IX. Influence of Method of Cooking on Vitamin C Content of Cabbage, *Food Research* 3: 311 (May-June) 1938.

14. Fenton, Faith; Tressler, D. K.; Camp, S. C., and King, C. G. Losses of Vitamin C During Boiling and Steaming Carrots, *Food Research* 3: 403 (July-Aug.) 1938.

15. Mayfield, Helen L., and Richardson, Jessie E.: Ascorbic Acid Content of Parsnips, *Food Research* 5: 361 (July-Aug.) 1940.

16. Harris, R. S.; Wissmann, H. B., and Greenlie, David: The Effect of Reduced Evaporation on the Vitamin Content of Fresh Vegetables in Refrigerated Storage, *J. Lab. & Clin. Med.* 25: 538 (May) 1940.

17. Fitzgerald, G. A., and Fellers, C. R.: Carotene and Ascorbic Acid Content of Fresh Market and Commercially Frozen Fruits and Vegetables. *Food Research* 3: 109 (Jan.-April) 1938.

hundred grams (table 2). Spinach¹⁸ at from 1 to 3 C. lost its vitamin C very slowly, whereas at room temperature it lost half in three days and nearly all in seven days. Peas,¹⁹ on the other hand, showed no appreciable loss of vitamin C in six days at 1 to 9 C. but considerable at 18 to 22 C. Lima beans,²⁰ shelled and unshelled, at 0 C. for eleven days lost respectively 58 and 31 per cent of their vitamin C content. Sweet corn²¹ purchased on the market does not suffer a significant loss in vitamin C during its good quality history. Fresh corn cooked on the cob for eating (twelve minutes) lost 7 to 10 per cent of its vitamin C content. Mack, Tapley and King²² reported that wax beans lost 81 per cent and Kentucky Wonder 58 per cent vitamin C in six days at from 21 to 23 C. and proportionately less in shorter periods. When wax beans were cooked to the done stage there was 62 per cent of the vitamin C in the drained solids and 26 per cent in the cooking water. The corresponding figures for Kentucky Wonder beans were 66 and 32, indicating a destruction of 12 and 2 per cent respectively.

Wheeler, Tressler and King²³ found that the ascorbic acid content of parsnips stored over winter in a pit dropped from 40 mg. per hundred grams in the fall to 15 mg. in the spring. Kale and New Zealand spinach lost half in four days at room temperature, while the loss in broccoli and cauliflower was only moderate. Wilting is always accompanied by serious loss of vitamin C.

Richardson and Mayfield²⁴ state that canned citrus juices and tomato juice after the can is opened lose no vitamin C in forty-eight hours, stored in a refrigerator.

18. Tressler, D. K.; Mack, G. L., and King, C. G.: Vitamin C Content of Vegetables: I. Spinach, *Food Research* 1: 3 (Jan.-Feb.) 1936.

19. Mack, G. L.; Tressler, D. K., and King, C. G.: Vitamin C Content of Vegetables: II. Peas, *Food Research* 1: 231 (May-June) 1936.

20. Tressler, D. K.; Mack, G. L.; Jenkins, R. R., and King, C. G.: Vitamin C in Vegetables: VII. Lima Beans, *Food Research* 2: 175 (March-April) 1937.

21. Dunker, C. F.; Fellers, C. R., and Fitzgerald, G. A.: Stability of Vitamin C in Sweet Corn to Shipping, Freezing and Canning, *Food Research* 2: 41 (Jan.-Feb.) 1937.

22. Mack, G. L.; Tapley, W. T., and King, C. G.: Vitamin C in Vegetables: X. Snap Beans, *Food Research* 4: 309 (July-Aug.) 1939.

23. Wheeler, Katherine; Tressler, D. K., and King, C. G.: Vitamin C in Vegetables: XII. Broccoli, Cauliflower, Endive, Cantaloupe, Parsnips, New Zealand Spinach, Kohlrabi, Lettuce and Kale, *Food Research* 4: 593 (Nov.-Dec.) 1939.

24. Richardson, Jessie E., and Mayfield, Helen L.: The Vitamin C Content of Winter Fruits and Vegetables, *Montana State Bull.* 390, 1941. pp. 1-16.

On the other hand, Gould and Tressler²⁵ found that holding cooked cabbage at 1 to 3 C. resulted in a loss of 50 per cent vitamin C in twenty-eight hours. The relative stability of vitamin C under such conditions has been shown⁷ to be a characteristic of each product and not a function of the p_H or acidity, although influenced by them.

Bananas²⁶ in three stages of ripeness contained, green, 6.1 mg. of ascorbic acid per hundred grams; yellow, 6.3 mg., and fully ripe, 7.3 mg. House, Nelson and Haber²⁷ found no difference in the vitamin B₁ content of green, mature and vine ripened tomatoes, but the latter contained more vitamin A and vitamin C and more than the green mature picked tomatoes after they were ripened either in air or with ethylene.

TABLE 2.—Average Milligram Values for Ascorbic Acid per Hundred Grams

	Broccoli	Spinach	Peas	Asparagus	Snap Beans
As purchased on wholesale market.....	77	35.0	15.5	12.5	10.0
24 hours later at 70 F.	60	20.0	14.8	10.0	8.5
48 hours later at 70 F. . . .	50	18.5	14.0	10.0	7.5

Bartlett pears were shown by Tressler and Moyer²⁸ to drop from 9 to 4.9 mg. of ascorbic acid per hundred grams during the first two months of storage at 30 F. and thereafter fall but little.

While modern cold storage allows but little loss of food value as a consequence of respiration, Benoy²⁹ has pointed out that with vegetables harvested in summer this may be a matter of serious proportions. Benoy found that the carbon dioxide given off at 30 C. during the second to the twenty-sixth hour after being harvested accounted for a loss of several per cent of the sugar

25. Gould, Stella, and Tressler, D. K.: The Vitamin Content of Vegetables, *Food Research* 1: 429 (Sept.-Oct.) 1938.

26. Leverton, Ruth: Ascorbic Acid Content of Bananas at Three Stages During Ripening, *Food Research* 2: 59 (Jan.-Feb.) 1937.

27. House, Margaret C.; Nelson, P. Mabel, and Haber, E. S.: The Vitamin A, B and C Content of Artificially versus Naturally Ripened Tomatoes, *J. Biol. Chem.* 81: 495 (March) 1929.

28. Tressler, D. K., and Moyer, J. C.: Changes in Vitamin C Content of Bartlett Pears in Cold and Gas Storage, *Food Research* 6: 273 (July-Aug.) 1941.

29. Benoy, Marjorie, P.: The Respiration Factor in the Deterioration of Fresh Vegetables at Room Temperature, *J. Agric. Research* 39: 75 (July) 1929.

from vegetables as follows: asparagus 13.7 per cent, lettuce 6.4 per cent, green beans 6.3 per cent, okra 5.2 per cent, carrots 4.5 per cent, tomatoes 3.2 per cent and beets 2.7 per cent. The serious aspect of this loss is that the flavor loss is of even greater proportions.

Olliver³⁰ points out that while water soluble constituents tend to be extracted in the boiling of vegetables, this loss may be minimized and the extractives used by keeping the water at a minimum and using it. All the vitamin A and from 70 to 75 per cent of the vitamin B₁ is retained, and while from 40 to 75 per cent of the vitamin C may be extracted less than 10 per cent is actually destroyed. In the present war period, she points out, cooked vegetables constitute the chief source of vitamin C in England. While sodium, potassium and chlorine are extracted, they are dietetically unimportant, and calcium is not extracted.

It is evident from the array of evidence cited that storage, cooking and other treatments to which vegetables and fruits are subjected may have a material effect on their vitamin C value. It is evident also that these effects in many instances can be greatly minimized with care such as maintaining ideal storage and adopting appropriate cooking procedures. Heat in cooking is responsible for no serious vitamin C loss.

The reason for all these data presented on vitamin C is twofold. Of the vitamins, only in the case of C has it been possible to assay many foods by chemical means. Secondly, it is not uncommon, as Fenton³¹ has done, to use the retention of vitamin C in vegetables as a criterion of both quality and nutritive value in general.

EFFECT OF STORAGE AND COOKING ON OTHER NUTRIENTS

Data on nutritive value as affected by processing are not limited entirely to vitamin C. Aughey and Daniel³² report that there was no loss of thiamine in pressure cooking or boiling carrots; 16 per cent loss in baking potatoes; 20 per cent in pared and boiled potatoes; 22 per cent in boiled spinach; 9 per cent in simmered

30. Olliver, Mamie: *The Effect of Cooking on the Nutritive Value of Vegetables*, Chem. & Indust. 60: 586 (Aug.) 1941.

31. Fenton, Faith: *Vitamin C Retention as a Criterion of Quality and Nutritive Value in Vegetables*, J. Am. Dietet. A., June-July, 1940, pp. 524-535.

32. Aughey, Elizabeth, and Daniel, Esther P.: *Effect of Cooking upon the Thiamine Contents of Foods*, J. Nutrition 19: 285 (March) 1940.

green peas, and 22 per cent if soda is added; 18 per cent in boiled beans and 59 per cent if soda is added; no loss in boiled navy beans; no loss in rolled oats or wheat cooked in a double boiler; 14 per cent loss in baking bread; 15 per cent in braised pork loin, and 43 per cent loss in roast pork. Kelly and Porter³³ give, in international units of available thiamine per gram, values of variously prepared beans of two types (table 3). Their results are based on feeding experiments and it is noteworthy that all samples of beans with which they worked had a lower vitamin B₁ value in the raw state than in any of the cooked forms.

Lantz³⁴ found that neither the riboflavin nor the B₆ of pinto beans in the raw state was utilized by rats but

TABLE 3.—*International Units of Thiamine per Gram of Various Prepared Beans*

	Michigan Beans	Cranberry Beans
Raw	1.7	0.9
Boiled in soaking water.....	3.0	2.9
Boiled in fresh distilled water.....	2.9	2.8
Soaked with soda, boiled in fresh water.....	2.8	2.9
Baked in soaking water..	2.3	1.9

both were well utilized in the cooked beans. The cooked beans had 8 micrograms of riboflavin per gram, with negligible quantities in the cooking water.

Oldham and Schlutz³⁵ demonstrated that heating meat, as in cooking or drying, renders the total iron of beef muscle as available to infants as equivalent amounts of inorganic iron, whereas the iron of unheated lean meat is generally agreed to be but poorly utilized. Mickelsen, Waisman and Elvehjem³⁶ found nicotinic acid and riboflavin stable to most cooking processes in meats, and while thiamine suffers some loss it is least

33. Kelly, Eunice, and Porter, Thelma: Effect of Cooking upon the Vitamin B₁ Content of Two Types of Beans Grown in Michigan, Food Research 8: 85 (Jan.-Feb.) 1941.

34. Lantz, E. M.: Effect of Cooking on Riboflavin and Vitamin B₆ Content of Pinto Beans, New Mexico State Bull. 268, December 1939, pp. 1-16.

35. Oldham, Helen; Schlutz, F. W., and Morse, Minerva: Utilization of Organic and Inorganic Iron by the Normal Infant, Am. J. Dis. Child. 54: 252 (Aug.) 1937.

36. Mickelsen, O.; Waisman, K. A., and Elvehjem, C. A.: Recent Studies on the Vitamin Content of Meats and Meat Products, J. Am. Dietet. A. 15: 529 (Aug.-Sept.) 1937.

affected by frying in meat products. Hodson³⁷ found stewing, roasting, broiling or frying chicken had no effect on the riboflavin content.

BLANCHING FOR FROZEN AND CANNED FOODS

Many of the recorded experiments purporting to show the extraction effect of blanching are so far from actual conditions in commercial use that they are misleading. For example, Magoon and Culpepper³⁸ scalded 1,700 Gm. of spinach and peas in 16,000 cc. of boiling distilled water each for two and four minutes and green beans for four and eight minute periods. They state that in the case of spinach as much as 16 to 30 per cent of the total dry matter might under such conditions be extracted while, in the case of green beans, as little as 1.5 to 10 per cent was extracted, the values for peas lying in between. These, however, represent far more severe conditions than obtain in commercial blanching, in which a continuous stream of vegetables passes through a limited amount of water, which is replenished by the amount carried out by the vegetable. Under these conditions the proportion of water to vegetable is small and, obviously, the extractive effect thereby limited. Horner³⁹ noted that in blanching the losses of potassium ranged from 9 per cent in potatoes to 40 per cent in beans; phosphorus from 9 per cent in potatoes to 20 per cent in peas, and magnesium from 13 per cent in carrots to 25 per cent in peas and potatoes. Calcium is actually absorbed from the hard water used for blanching. As Olliver⁴⁰ has pointed out, extraction of potassium, sodium and magnesium is of no dietetic importance.

Some experiments on the extractive effect of blanching on the vitamin content are on record. Todhunter and Sparling's⁴⁰ values are given in table 4. Finke⁴¹

37. Hodson, A. Z.: Effect of Cooking on Riboflavin Content of Chicken Meat, *Food Research* 6:175 (March-April) 1941.

38. Magoon, C. A., and Culpepper, C. W.: Scalding, Precooking and Chilling as Preliminary Canning Operations, U. S. Department of Agriculture, Bulletin 1265, November 1924, p. 48.

39. Horner, G.: Progress Report on the Mineral Content of Canned Vegetables, University of Bristol Fruit and Vegetable Preservation Research Station, Campden, Ann., Sept. 1936-1937, pp. 51-56.

40. Todhunter, Elizabeth-Neige, and Sparling, B. L.: Vitamin Values of Garden Type Peas Preserved by the Frozen Pack Method, *Food Research* 3:489 (Sept.-Oct.) 1938.

41. Finke, Margaret L.: Vitamin Value of Garden Type Peas Preserved by Frozen Pack Method: III. Thiamine, *Food Research* 4:605 (Nov.-Dec.) 1939.

states that peas blanched for two minutes at 71 C. had 4 micrograms of thiamine per gram and only 2.6 when blanched two or three minutes at 99 C.

There is so much inconsistency in these figures that one is not warranted in drawing far reaching conclusions. When in one case the ascorbic acid is 9.1 mg. per hundred grams with a six minute blanch and only 7.2 with a four minute blanch, then there is no basis for assigning any significance to another case in which it is 22.6 for the six minute blanch while it is 23.2 for the four minute blanch. As for the thiamine values of Finke, it should be borne in mind that the feeding levels were 0.8 Gm. and 1.2 Gm. of peas a day and that the

TABLE 4.—*Extractive Effects of Blanching on Ascorbic Acid Content of Peas*

Time, Minutes	Blanch		Ascorbic Acid, Mg. per 100 Gm Peas
	Temperature	Kind	
1	99 C.	Water	21.0
2	99 C.	Water	18.5
3	99 C.	Water	17.0
1	99 C.	Steam	18.8
2	88 C.	Water	21.2
4	88 C.	Water	23.2
6	88 C.	Water	22.6
2	88 C.	Water	8.1
4	88 C.	Water	7.2
6	98 C.	Water	9.1

growth response for the 1.2 Gm. dosage was so great that it had to be discarded when the thiamine level was evaluated. Yet there is sufficient evidence to warrant the statement that the greater part of the loss of vitamin C in canning occurs before the vegetable enters the can. This is in part due to extraction and in part to destruction. The matter is not so simple in frozen vegetables.

FROZEN FOODS

In recent years so-called frosted or frozen foods have appeared in retail form. Long before, however, it was customary to freeze certain fruits, chiefly berries, in barrels with or without sugar, for the purpose of later converting them into jams, preserves and jellies. They were frozen without any precooking. When attempts were made to extend this freezing method to vegetables

it soon became apparent that their normal flavor could not long be retained. Vegetables so frozen soon acquire what is commonly referred to as a haylike flavor. This was traced to the effect of enzymes whose activity is not completely inhibited even in the frozen state. It is a well known fact that abnormal activity of enzymes is aroused in a broken, raw vegetable cell. While much has been said about "quick freezing" as a means of reducing the size of ice crystals that may otherwise pierce or rupture the cells, the fact of the case is that the rupturing of the raw vegetable cell cannot be avoided, irrespective of the rapidity with which freezing is accomplished. I was convinced of this experimentally in 1928 by the use of liquid air as a freezing medium. So-called quick freezing of vegetables has virtues only in that it reduces the development of micro-organisms as well as the action of atmospheric oxygen on the food, for example, on vitamin C.

It is now customary to blanch all vegetables before freezing to inactivate the enzymes and, for canning, blanching is necessary to expel air to avoid straining the hermetic seal in processing and to reduce the volume and enable compact filling. Temperatures up to or less than boiling water for one to a few minutes have been found adequate.

The gases in most vegetables are relatively low in oxygen content in comparison with the oxygen of the air, owing to the fact that the respiratory process constantly taking place in raw vegetables tends to use up the oxygen within the tissues. The blanching, as can be surmised from the relatively low loss of vitamin C in cooking vegetables, has no serious destructive effect on vitamins.

However, after the vegetables are blanched their oxygen-consuming enzymes are inactivated. Glutathione and hydrogenases in them no longer exert their reducing effect.⁷ The vegetables now become saturated with oxygen; this oxygen becomes a serious agent in vitamin C loss with storage if low temperatures are not at all times maintained. This is a matter of particular concern if frozen vegetables are thawed an appreciable time before being used. As the vegetables must be cooked for table use, the vitamin C may now suffer a greater loss than when raw vegetables are cooked directly for table use.

Rose,⁴² who reviewed the literature on frozen foods, has pointed out the importance of their being kept in the frozen state up to the time they are to be cooked for use. Fellers and Stepat⁴³ found the average ascorbic acid content of thirteen samples of frozen peas to be 13.1 mg. per hundred grams, but after they had been defrosted from two to six hours the average value dropped to 4.1 mg. Todhunter and Sparling⁴⁰ claimed that peas thawed within thirty minutes lost 27 per cent in one hour thereafter. At 4.5 C. 25 per cent was lost in twenty-four hours. This represents keeping the peas in a refrigerator for thawing. Jenkins and Tressler⁴⁴ reported losses from negligible to 20 per cent in six months at 0 F. and much higher losses at 10 to 15 F., ranging from approximately 40 per cent to more than 90 per cent in various products. McIntosh and Tressler⁴⁵ found a variable loss of vitamin C up to 14 per cent in cooking a number of frozen vegetables for table use in various ways with from 13 to 30 per cent in the liquor and from 70 to 80 per cent in the solids, the amount in the liquid depending on the amount of cooking water.

It appears from these data and others that it is important not only to freeze vegetables quickly but to maintain a low storage temperature and to prevent thawing until such time as they are to be cooked for the table.

CANNING

Canning was the first method of preserving foods to receive scientific study. The latest report of the National Resources Planning Board states "No better example of the value to be obtained from a trade association's operation of its own technical research laboratory can be cited. . . . The industry quickly availed itself of the association laboratory's findings and put its recommendations into effect in processing. . . . The industry has benefited in many ways, . . . the public has benefited through having made available a

42. Rose, Mary Swartz: The Effect of Quick Freezing on the Nutritive Value of Foods, *J. A. M. A.* **114**: 1356 (April 6) 1940.

43. Fellers, C. R., and Stepat, W.: Effect of Shipping, Freezing and Canning on the Ascorbic Acid Content of Peas, *Proc. Am. Soc. Horticultural Science* **33**: 627, 1935.

44. Jenkins, R. R.; Tressler, D. K.; Moyer, J., and McIntosh, Jennie: Vitamin C Experiments, *Refriger. Engin.* **39**: 381 (June) 1940.

45. McIntosh, Jennie A., and Tressler, D. K.: The Effect of Different Cooking Methods on the Vitamin C Content of Quick Frozen Vegetables, *J. Home Econ.* **32**: 692 (Dec.) 1940.

very wide variety of wholesome foods at lower costs." In another connection the report states "The production of vegetables suitable for canning has inspired some lines of important research." Agricultural experiment stations of many states have had a hand in developing varieties especially suitable for canning. Canning factories are located in the center or vicinity of the areas supplying them. Deterioration of raw produce due to storage is not a problem. Each crop may be harvested when it is at its prime. No allowance need be made for ripening in transit, thus permitting full development on tree or vine.

The chief feature in canning foods is the application of sufficient heat to destroy spoilage organisms. This in many cases is more than is necessary for table use. One of the most notable effects is the change in green vegetables from a bright green to an olive green. This has been in part linked ⁴⁶ to a lowering of the p_H value which generally occurs in cooking foods, the degree depending on the time and temperature. Since chlorophyll has never been found to possess nutritional functions, nor the change in p_H to have any nutritional significance, these effects need not be discussed here.

Fixsen ⁴⁷ has tabulated effects of cooking and canning. That processing is without effect on vitamin A is evidenced by the experiments of Steenbock and Boutwell, ⁴⁸ who autoclaved yellow maize, chard, carrots, sweet potatoes, squash and alfalfa for three hours at 250 F. without affecting the vitamin A. This is far more severe than any canning process.

Arnold and Elvehjem ⁴⁹ studied the effect of processing dog food meat in 1 pound cans. The following thiamine losses were noted in a process of two hours at 240 F.: beef kidney 80 per cent, beef lung 75 per cent, and beef spleen 70 per cent. Leg muscle in one hour and fifty minutes at 250 F. lost 80 per cent. In a sample of "meat food product" which "contained a small amount of grains" the following losses were noted: at 240 F. in one hour 60 per cent, in one and

46. Blair, J. S.: Color Stabilization of Green Vegetables, U. S. Patent 2,186,003, Jan. 9, 1940.

47. Fixsen, Margaret A. Boas: The Vitamin Content of Human Foods as Affected by Processes of Cooking and Canning, *Nutrition Abstr. & Rev.* 8: 281-307 (Oct.) 1938.

48. Steenbock, H. A., and Boutwell, P. W.: Fat-Soluble Vitamin, *J. Biol. Chem.* 41: 163 (Feb.) 1920.

49. Arnold, A., and Elvehjem, C. A.: Processing and Thiamine, *Food Research* 4: 547 (Nov.-Dec.) 1939.

one-half hours 67 per cent, in two hours 70 per cent, in one hour and fifty minutes at 250 F. 80 per cent. An interesting feature of these data is that doubling the process time raised the destruction only from 60 to 70 per cent, yet the product received a more severe heat treatment during the second hour because a considerable part of the first hour was required for the heat to penetrate the material in the can. The necessary processing time for such a product lies between one and two hours. The p_H of these products was between 6 and 7, whereas that of vegetables is approximately one p_H unit lower and the stability toward heat is much greater at the lower p_H . With lower p_H and better heat penetration for most vegetables the process is correspondingly less severe. In the absence of direct data on the various vegetables it may be inferred that destruction of vitamin B₁ in general canning is far less than the losses cited.

Schlutz and Knott⁵⁰ tested four lots of milk by feeding experiments before and immediately after evaporation and canning and found respectively 34, 24, 21 and 20 per cent losses. One sample, which contained 80 international units per quart when first canned, contained 68 after two months' storage and 59 international units after four months. Two other samples, which lost originally 20 and 21 per cent of their B₁, with eight months' storage lost an additional 37 and 42 per cent respectively.

The best evidence of the stability of vitamin C to the heat of canning is the fact, such as described with tomato juice, that many foods when heated with dehydroascorbic acid will actually reduce it to ascorbic acid. This explains many of the observations of McHenry and Graham⁵¹ and others that heating, in the case of several vegetables, increased the titration value toward 2,6-dichlorophenolindophenol. Unsuccessful attempts have been made to explain such phenomena on the basis that ascorbic acid is in part held in some complex combination, and this heating hydrolyzes it. Many foods when processed in the can actually have a higher titration value after the process. Doubling the com-

50. Schlutz, F. W., and Knott, Elizabeth M.: Factors Affecting the Vitamin B₁ Content of Evaporated Milk, *Soc. Exper. Biol. & Med.* **40**: 532 (April) 1939.

51. McHenry, E. W., and Graham, Murray: Observations on the Estimation of Ascorbic Acid by Titration, *Biochem. J.* **29**: 2013 (Sept.) 1935.

mercial process of canned peas⁵² from twenty-five to fifty minutes at 250 F. did not lower their value as an antiscorbutic for guinea pigs. Tomatoes⁵³ and apples⁵⁴ were shown to suffer no loss of ascorbic acid in canning, although it was necessary to deplete the apples of oxygen by the so-called soaking process already referred to.⁵⁵

Perhaps the most significant data on the nutritional value of canned foods has been obtained in a number of experiments in which a diet entirely of canned foods was fed. While it may be said, with whatever justification, that human beings over many generations have adapted themselves to a cooked food diet, this cannot be said of rats and guinea pigs. Yet both species of animals, the rats over ten generations and the guinea pigs over seven, thrived better on a canned food diet than on a diet of similar foods uncooked, according to Kohman, Eddy, White and Sanborn.⁵⁶ Foods for these experiments were purchased in the New York City markets as they would be for family use.

Cooking of foods renders the calcium more available. The vitamin A of foods like peas and spinach has been found to be more readily available after cooking. Reference has already been made to such an effect on vitamin B₁ and riboflavin in various beans. The protein of all legumes is improved nutritively by being subjected to heat.

In France Cheftel,⁵⁴ after feeding rats canned and noncanned foods over a period of fourteen generations, reported that when individuals of the two groups were put on a vitamin A-free diet at the Pasteur Institute those having been raised on canned foods showed the first symptoms of vitamin A deficiency two weeks later than those raised on noncanned foods.

Godden⁵⁵ in Great Britain fed, on a comparable basis, (1) drained canned foods, (2) total canned foods (solid and liquid) and (3) home cooked foods from which the cooking water was discarded. On a basis of repro-

52. Kohman, E. F.; Eddy, W. H., and Guerin, Celia Zall: Canning of Tomato Juice Without Vitamin C Loss, *Indust. & Engin. Chem.* **25**: 682 (June) 1933.

53. Kohman, E. F.; Eddy, W. H.; White, Mary Elizabeth, and Sanborn, N. H.: Comparative Experiments with Raw, Home Cooked and Canned Food Diets, *J. Nutrition* **14**: 9 (July) 1937.

54. Cheftel, H.: Nutritional Value of Canned Foods, *Food* **7**: 47 (Nov.) 1937.

55. Godden, W.: Nutritive Value of Canned Foods in Great Britain, *Food* **7**: 48 (Nov.) 1937.

duction, milk supply and growth, the first and last diets yielded comparable results but the canned food diet with the liquor included was unsatisfactory because of its bulkiness. This difficulty is in evidence only when too much of the diet is made up with foods with considerable liquid. The matter can readily be corrected by inclusion of higher calory foods such as pork and beans, macaroni and cheese, and brown bread, all of which are readily available in canned form. Subsequently, Godden and Thomson⁵⁶ made many observations over several generations on canned and uncanned foods and found no basis for distinguishing between the two.

A word is in order regarding the containers for canned foods. Daniels and Rutherford⁵⁷ claim better vitamin preservation in tin than in glass. Fellers and Buck⁵⁸ point out that entrapped oxygen in commercially packed puréed peas, spinach and tomato juice may not disappear until twenty to sixty days after being packed in glass. Vitamin losses occurred mostly during this period and relatively little after six months. Glass covers for glass containers are of necessity dome shaped, and this inevitably entraps more air than the cover of the tin can. Commercial canning minimizes this entrapped air in glass canning by vacuum closure, which the home canners cannot employ.

It may be added that traces of entrapped air in tin cans disappear completely within twenty-four hours in a plain can but may persist for several days in an enameled can. This prompt disappearance of oxygen in a tin can is a consequence of the high reduction potential of the film of nascent hydrogen with which tin in contact with foods coats itself. This film is of great value both in furnishing a reducing atmosphere and in furnishing protection for the tin against the action of the food on it.

DEHYDRATION

Dehydration is limited largely to a few fruits—prunes, raisins, peaches, apples, apricots, figs, dates and the like. Vitamin C suffers almost complete destruction in

56. Godden, W., and Thomson, W.: The Nutritive Value of Canned Foods, *J. Soc. Chem. Ind.* **58**: 81 (March) 1939.

57. Daniels, Esther P., and Rutherford, M. B.: Effect of Home Canning and Storage on Ascorbic Acid Content of Tomatoes, *Food Research* **1**: 341 (July-Aug.) 1936.

58. Fellers, C. R., and Buck, R. E.: Retention of Vitamins C and A in Glass Packed Foods, *Food Research* **6**: 135 (March-April) 1941.

most dehydrated products. The vitamin C protective effect of sulfuring (to prevent darkening of the light colored fruits) was shown by Morgan, Field and Nichols.⁵⁹ This same sulfuring process may, however, prove to be as destructive to vitamin B₁ as it is protective for vitamin C. When first sulfured, the fruits may contain sulfur dioxide from 2,500 to 10,000 parts per million. The splitting of thiamine into its thiazole and pyrimidine components by sulfur dioxide was the clue to its identification. The quantitative determination of thiamine by the microbiologic (yeast) method has as its basis the complete splitting of its molecule by sulfite. Treatment with sulfur dioxide is one means of preparing a vitamin B₁ free diet for experimental work.

Dehydration of vegetables, usually stimulated during wartime, has not met with a high degree of satisfaction as yet, so far as is reported. In most cases the flavor changes are too pronounced. Rancid and haylike flavors commonly develop. Dehydration of eggs and of milk, particularly skim milk, is proving very useful, and according to recent reports this is true also of lean meat. Since moisture free butter fat stores well, it makes possible, with dehydrated skim milk, to have reconstituted milk suitable for many purposes. While the nutritive value of dehydrated vegetables for food for human beings seems not to have been given especial attention, some deductions may be made. Fraps and Kemmerer⁶⁰ found that when fish oils are mixed with poultry feed from 79 to 100 per cent of the vitamin A is lost within a month. Taylor and Russell⁶¹ state that dried and chopped alfalfa hay stored in a bag lost 50 per cent of its carotene content in three months and the remaining carotene became less potent. In this connection it is interesting to note that even in raw carrots a tenfold variation in carotene and depth of color has been accompanied by little more than a twofold variation in vitamin A potency. It is thus possible that dehydrated vegetables retain their vitamin A values but poorly, and there is ample evidence that vitamin C is

59. Morgan, Agnes Fay, Field, Anna, and Nichols, P. F.: The Effect of Cooking on the Vitamin A and C Content of Fresh and Dried Apricots, *J. Agric. Research* **46**: 841 (May) 1933.

60. Fraps, G. S., and Kemmerer, A. R.: Losses of Vitamin A and Carotene from Feeds During Storage, *Texas Agric. Exper. Sta. Bull.* 557, 1937, pp. 1-27.

61. Taylor, M. W., and Russel, W. C.: The Stability of Carotene in Plant Tissues, *J. Nutrition* **16**: 1 (July) 1938.

almost completely lost. In recent developments, vegetables are being blanched before dehydration. It is still problematic what will be the effect of the blanch.

MISCELLANEOUS PROCESSES

The distinctly inferior nutritive value of bleached vegetables is not commonly realized. Plant breeding has produced firmer heads of lettuce and cabbage and less green on celery, but Crist and Dye⁶² have pointed out that the green outer leaves are many times richer not only in vitamin A but also in nearly all the mineral elements. They are known to be richer in vitamin C also, and probably in other vitamins as well. It is fortunate, therefore, that in recent years green asparagus for canning has become more popular.

The legal standards for jellies, jams and preserves demand a minimum of 45 pounds of fruit to 55 pounds of sugar. The final product must have a minimum of 65 per cent solids in the case of certain fruits and 68 per cent in others. This makes it necessary to evaporate about 10 per cent of the water in the fruit in the process of making conserves. In commercial practice this requires a relatively short time and ascorbic acid losses may be 10 to 15 per cent, and under vacuum even less. There is some evidence that the sugar has a stabilizing effect on ascorbic acid. Further than this little information on nutritive value is available except that the high sugar content makes the caloric value of conserves overshadow other nutrients.

From various foreign countries come reports of the importance of conserves in this emergency as vitamin C sources by making possible the utilization of heretofore little used items, chief of which are rose hips. Not all rose hips are rich in vitamin C, however. Some contain only a few milligrams of ascorbic acid per hundred grams, some are equal to and others several times as rich as tomatoes.

Pyke and Melville^{62a} list a maximum of 1870 mg. per 100 grams (1.87 per cent). Green walnuts are also listed as a potent source of vitamin C, which, in the form

62. Crist, J. W., and Dye, Marie: The Association of Vitamin A with Greenness in Plant Tissue, *J. Biol. Chem.* **81**: 525 (March) 1929.

62a. Pyke, M., and Melville, R.: Vitamin C in Rose Hips, *Biochem. Jour.* **36**: 336-9, April, 1942.

of their preserves, appears to be quite stable since it is reported that preserves made in 1940 had in August 1942 the following values:

Green pickled walnuts.....	1,080 mg. per 100 Gm.
White pickled walnuts.....	1,070 mg. per 100 Gm.
Walnut marmalade	630 mg. per 100 Gm.
Walnut and black currant jam.....	520 mg. per 100 Gm.
Walnut and green tomato chutney .	410 mg per 100 Gm.

During the siege of Leningrad many such unusual sources of vitamin C were used, including pine needle concoctions. That the antiscorbutic potency of pine needles is a recent discovery is erroneous however. Francis Parkman^{62b} is authority for the information that the American Indian demonstrated their value in this connection to early French explorers 400 years ago.

Spoilage is prevented in dehydrated foods because they lack the water necessary for micro-organisms. In conserves the high sugar content makes the water unavailable by osmosis. Because of its smaller molecule, much smaller percentages of sodium chloride will preserve foods, but in removing excess salt soluble food constituents are removed.

The hydrogenation process has made available for human consumption much vegetable fat. From the work of Hoagland and Snider⁶³ and of Sherman⁶⁴ it is to be inferred that hydrogenation lowers the digestive coefficient and that the loss of unsaturation causes inferiority as respects other nutritive phases. That this is of any practical dietary significance is not known.

Ethylene treatment of fruits is not believed to influence any nutritional quality. It merely hastens processes already taking place.

The baking of bread is said by Hoffman, Schweitzer and Dalby⁶⁵ to result in a loss of from 5 to 9 per cent of the thiamine content. This loss occurs largely in the crust. Toasting causes another loss, ranging from 12 to 24 per cent.

Losses from toasting may be of greater significance than losses in baking in some instances since Downs &

62b. Parkman, Francis: *Pioneers of France in the New World*, 17th Ed. Pp. 194-5. Boston: Little, Brown and Company, 1880.

63. Hoagland, R., and Snider, G. G.: *Nutritive Properties of Steam-Rendered Lard and Hydrogenated Cotton Seed Oil*, *J. Nutrition* **22**: 65 (July) 1941.

64. Sherman, W. C.: *The Effect of Certain Fats and Unsaturated Fatty Acids upon the Utilization of Carotene*, *J. Nutrition* **22**: 153 (Aug.) 1941.

65. Hoffman, Charles; Schweitzer, T. R., and Dalby, Gaston: *The Loss of Thiamine in Bread in Baking and Toasting*, *Cereal Chemistry* **17**: 737 (Nov.) 1940.

Meckel ^{65a} report that in some areas 35% of the bread is eaten as toast, while many eat toast almost exclusively. They give the following losses for varying toasting times, 50 second toast being preferred by 8 out of 10.

There is no evidence that fermentation, as occurs in the making of sauerkraut, in pickling or in wine making, has a specific effect on any of the vitamins; nor are the vitamins in any fermented product any less subject to adverse conditions than they are in the unfermented.

Some claims have been made that salt has a protective effect on ascorbic acid in cooking vegetables. These are based mainly on the work of Hoygaard and Rasmussen ^{65b} who cooked only three products and those in the proportion of 10 grams in 200 ml. of water. Their limited results are insignificant. Any evidence they might indicate to some is overshadowed by the

Percentage Thiamine Loss in Toasted Bread

Seconds	White Unenriched	White Enriched	Whole Wheat
30	9.2	5.2	4.0
50	19.7	13.0	12.5
70	31.4	17.0	21.0

results of Snow and Zilva ^{65c} who found sodium chloride catalysed the oxidation of ascorbic acid to 131% and potassium iodide to 178% over that which occurred when these salts were not present. Innumerable experiments to determine the destruction of ascorbic acid in cooking vegetables have been made. If salt had any appreciable effect in practical vegetable cookery, it is to be supposed that some investigator would certainly have brought it out.

CONCLUSIONS

Modern methods of food distribution supply us with vegetables and fruits of numerous varieties in many forms. Vegetation extracts minerals from the earth, usually in suitable proportions, and synthesizes our

^{65a}. Downs, David E., and Meckel, R. B.: Thiamine Losses in Toasting Bread, *Cereal Chem.* **20**:352-5, May, 1943.

^{65b}. Hoygaard, A., and Rasmussen, H. Waage: Inhibiting Effect of Sodium Chloride on the Oxidation of Ascorbic Acid, *Nature* **142**: 293, Aug. 13, 1938.

^{65c}. Snow, C. A., and Zilva, S. S.: The Catalytic Oxidation of Ascorbic Acid in Presence of Tea Infusions, *Biochem. Jour.* **36**: 641 (Sept.) 1942.

vitamin supply. Until subjected to heat, fruit and vegetables are live tissue and as such constantly undergo changes, some of which are detrimental. Methods have been devised to limit such changes, but whether it is for storage, frozen, dehydrated or canned foods, there still remains work to be done to ascertain more definitely the extent of changes that take place for each type of commodity under the various conditions to which it may be subjected and to find ways of minimizing still further undesirable changes. It is obvious even now that to use vegetables and fruits generously in our diets is in accord with our aims in nutrition today.

CHAPTER XVI

IMPROVING THE QUALITY OF CHEAP STAPLE FOODS

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Discoveries in the science of nutrition over the past three decades have made it possible to state more exactly than ever before the many specific factors that are essential for satisfactory nutrition. A brief classification of them would include food energy, the protein factor, essential fatty acids, indispensable mineral nutrients and the vitamins. An attempt to list individually all the substances required gives a total of approximately forty, the exact number depending on whether the claims for the existence of certain factors are to be accepted or not. In view of this new knowledge it is obvious that foods can now be evaluated in a manner much more precise and specific than was ever possible before. These recent discoveries have also included the isolation and finally synthesis on a commercial scale of several of the vitamins, thus making it possible to add these factors to foods. Such possibilities have naturally received the attention of both the food industry and students of nutrition and public health. On the industrial side it has been necessary to solve many technological problems. Nutritionists, clinicians and governmental agencies faced with these possibilities have naturally interested themselves in the formulation of principles to be followed in such addition of special factors to foods, amounts to be added and related topics.

The application of these new discoveries can of course result in the production of new foods that would doubtless be classified for some time at least as novelties or specialties because of their relatively high cost and only slight use by the mass of the population. In contrast to this, and much more important for public health and preventive medicine, is the application that means definite improvement in the quality of cheap staple foods that occupy prominent places in the dietary. To the extent that these staples, already endowed with a high consumer appeal and acceptance, can be nutri-

tionally improved, the chances of incidence of diseases that represent dietary shortcomings can be reduced and the cause of public health thus advanced. This article deals with the latter possibility.

THE GRAINS

Discussions of the foods that figure prominently in various dietaries throughout the world, therefore staple foods,¹ usually deal with them in terms of their contribution to the energy needs of the population. The cheapest source of food energy in the diets used throughout the world is the cereal grains. In the United States the two cheapest sources of calories are cereal products and cane sugar. In southern China and certain other parts of the Orient rice is the most economical and readily available food and therefore the most widely used cereal. From the standpoint of worldwide use rice comes first; this cereal is eaten by more people than any other member of the cereal grain group. The dominant cereal used as human food in the United States is wheat.

The greater keeping qualities of milled cereals in contrast to the whole grain, together with the exigencies of modern civilized life such as ease of transportation over long distances, has resulted in some degree of milling of the grain becoming the established custom, a practice which, from the standpoint of nutritive value of the material, means loss in corresponding degree. It is not surprising, therefore, that the addition of essential vitamins and minerals to milled cereal products, wheat flour for example, should have received serious attention as one of the new possibilities for application of modern nutritional knowledge in the interest of preventive medicine.²

Interest in this possibility of improving the nutritive value of wheat flour has finally resulted in the establishment by the Food and Drug Administration of the federal government of standards for enriched flour.³ The standards established in 1941 were modified in July, 1943. The data given in table 1 are based on the

1. Bennett, M. R.: Wheat in National Diets, Wheat Studies of the Food Research Institute, Stanford University 18: 37-76 (Oct.) 1941.

2. Cowgill, G. R.: The Need for the Addition of Vitamin B₁ to Staple American Foods, J. A. M. A. 113: 2146-2151 (Dec. 9) 1939.

3. Definitions and Standards of Identity for Flour and Related Products, Federal Register 6: 2574-2582 (May 27) 1941. Wheat Flour and Related Products: Amendments to Definitions and Standards of Identity, Federal Register 8: 9115-9116 (July 3) 1943.

1943 amendments to the original order. Current standards for enrichment or fortification of other foods are also given in this table.

Enforcement of the regulation with respect to enrichment of flour with riboflavin has been delayed until Oct. 1, 1943 because of shortage of this vitamin owing to lack of satisfactory methods for production of it on a sufficiently large industrial scale.

TABLE 1.—*Current Standards for Enrichment and Fortification of Foods*

Enriched White Flour ³ (Required):

Thiamine.....	From 2.0 to 2.5 mg. per pound
Riboflavin.....	From 1.2 to 1.5 mg. per pound
Nicotinic acid (niacin) or its amide.....	From 16 to 20 mg. per pound
Iron.....	From 18 to 16.5 mg. per pound

Enriched White Flour (Optional):

Vitamin D.....	From 250 to 1,000 U. S. P. units per pound
Calcium.....	From 500 to 625 mg. per pound
Wheat germ.....	Not more than 5 per cent

Oleomargarine Fortified with Vitamin A (Federal Register 6:2761 [June 7] 1941):

Not less than 9,000 U. S. P. units of vitamin A per pound

Milk Fortified with Vitamin D:

Council on Foods and Nutrition of A. M. A. approves milk containing from 135 to 400 U. S. P. units per fluid quart or reconstituted quart

Iodized Table Salt:

Council on Foods and Nutrition of A. M. A. accepts salt containing 0.01 per cent of potassium iodide or equivalent of sodium iodide, provided distribution of the iodide in the salt is uniform and this concentration is present after storage under ordinary conditions. Food and Nutrition Board of National Research Council also has approved of this standard

Discussion of this "enrichment" or fortification problem has brought out many suggestions of principles and facts to be considered when making additions of vitamins and minerals to foods.⁴ It is pertinent to inquire whether a lack of the dietary essential in question in the ordinary diet of the people is sufficiently widespread to justify the proposed addition of it to appropriate foods. If no real need for such addition can be shown,

4. The Fortification of Foods with Vitamins and Minerals. A Symposium held at the American Institute of Nutrition, Toronto, Ontario, April 26, 1939. Published in the *Milbank Memorial Fund Quarterly* 17: 221-262 (July) 1939. American Institute of Nutrition, Symposium on Fortified Food, April 1, 1942. Published in *Federation Proceedings* 1: 324-351 (Sept.) 1942.

one may well question the wisdom of it as a socially planned and directed move; its chief justification then becomes a commercial one dependent for its success almost entirely on advertising and other promotional activities of units of the food industry.

If there are reasonable grounds for believing that a serious deficiency of the dietary factor of interest does exist, the question arises as to the most suitable food to be "enriched" or fortified with it. There may be rather general agreement as to the class of food to be enriched, but it does not necessarily follow that all products in this class should be so treated. As an example of this situation consider macaroni, which is made largely of wheat flour. Macaroni is always boiled when being prepared for the table, and tests have shown that such handling results in loss of a considerable part of added vitamin B₁. Therefore, even if the pure vitamin can be obtained at practically negligible cost, so that relatively large amounts more than sufficient to offset such loss can be added, one may well question the practicality of its addition to macaroni. As another example one may consider the fortification of lard with vitamin A. Since this animal fat is widely used in cooking and such use results in appreciable loss of the vitamin, a conservative attitude toward the question of the addition of vitamin A to lard is justified. In the light of these two illustrations it is obvious that a body of facts regarding the need for various dietary essentials and the probable supply in common foods is required, as well as information of the technological sort concerning the feasibility of the proposed addition to any given food product before approval should be given any specific proposal of enrichment or fortification.

Concerning this question of need for particular dietary factors by the American people, numerous papers may now be cited. Students of nutrition have long agreed with Sherman that there is a real likelihood of a significant deficiency of calcium, and therefore there is justification for promoting wider use of calcium rich foods like milk, milk products and green leafy vegetables. There are also reasons for believing that the American diet is not as rich in thiamine as it should be.² The testimony offered in the hearings held by the Food and Drug Administration which resulted in the federal standards for enriched flour supported the view

that the average American dietary does not furnish amounts of some essential vitamins and minerals sufficient to insure the public health. On the basis of the evidence they have summarized concerning the existence of malnutrition in our population, Jolliffe, McLester and Sherman⁵ believe that such malnutrition is sufficiently widespread to justify taking measures to obviate it.

VITAMINS AND MINERALS

In 1939 the Council on Foods and Nutrition of the American Medical Association considered this general question of the addition of vitamins and minerals to foods and adopted the following statement as an expression of its policy:

The Council on Foods desires to encourage the restorative addition of vitamins or minerals or other dietary essentials, in such amounts as will raise the content of vitamin or mineral or other dietary essential of general purpose foods to recognized high natural levels; with the provision that such additions are to be limited to vitamins or minerals or other dietary essentials, *for which a wider distribution is considered by the Council to be in the interest of the public health.*⁶

The words that I have italicized are particularly pertinent here, because they state an important limitation which not only the Council has adopted, when expressing its approval of such additions, but the Committee on Food and Nutrition (now Food and Nutrition Board) of the National Research Council as well.

In its approach to this problem the Council on Foods and Nutrition of the American Medical Association deemed it advisable to express the limitations of additions of various factors to general purpose foods in terms of milligrams per hundred calories and established such limitations with respect to calcium, iron, thiamine, riboflavin and niacin. The values are presented in table 2.

The Committee on Food and Nutrition of the National Research Council expressed its views on this question in the following resolution:

WHEREAS, There exist deficiencies of vitamins and minerals in the diets of significant segments of the population of the

5. Jolliffe, Norman; McLester, J. S., and Sherman, H. C.: The Prevalence of Malnutrition, J. A. M. A. 118: 944-950 (March 21) 1942.

6. Annual Meeting of the Council on Foods, J. A. M. A. 118: 680 (Aug. 19) 1939.

United States which cannot promptly be corrected by public education in the proper choices of foods, be it resolved in order to correct and prevent such deficiencies:

1. That the Committee endorses the addition of specific nutrients to staple foods (as indicated under 6 below) which are effective vehicles for correcting the above deficiencies in the diets of the general population, or of significant advantage of geographic, economic or racial segments thereof;

2. That the Committee opposes the inclusion of additions of specific nutrients under definitions and standards which may be promulgated under the Food, Drug and Cosmetic Act, except in the case of foods which constitute such effective vehicles of distribution;

3. That the Committee favors unequivocally the fulfilment of the nutritional needs of the people by the use of natural foods as far as practicable and to that end encourages education in the proper choice of foods and the betterment of processes of food manufacturing and preparation so as to more fully retain the essential nutrients needed thereto;

4. That, to avoid undue artificiality of food, the Committee favors, whenever practicable, the choice, as vehicles for the corrective distribution of vitamins and minerals, of those foods which have suffered losses in refining processes and recommends that the vitamins and minerals added to such foods should preferably be the kinds and quantities native therein in the unrefined state;

5. That the addition of other than natural levels of vitamins and minerals to foods which are suitable as vehicles of distribution may be sanctioned when more natural routes are practically unavailable as ways to correct known nutritional deficiencies;

6. That, at present, the Committee favors appropriate enrichment of flour and bread (and perhaps corn meal), the fortification of milk with vitamin D, the suitable addition of vitamin A to table fats and of iodine to salt for dietary use. There is no information available to the Committee at the present time which indicates that it is desirable for the Committee to recommend the addition of vitamins or minerals to foods other than those named;

7. That, specifically, the Committee opposes the addition of synthetic vitamins to carbonated beverages and confectionery.

From the statement quoted it is evident that the idea of adding vitamins and minerals, or other dietary essentials, to foods has been accepted sufficiently to secure official sanction in the following cases: the appropriate enrichment of flour and bread (and perhaps other cereal products) with several factors, the fortification of milk with vitamin D, of table fats with vitamin A, and of

table salt with iodine. To what extent other additions will finally acquire widespread acceptance and then official approval, only time and the accumulation of new data can determine.

When it has been agreed that certain dietary essentials may well be added to particular foods or classes of foods, the question arises as to how much should be added. The discussion of this problem has been most interesting to follow. It has been argued that a worthwhile principle to apply is that of restoration of the milled or processed food by appropriate addition of dietary factors to give a product approximating the natural food source, whole wheat flour for example as contrasted with highly milled white flour. This has

TABLE 2.—*Important Food Values of Natural Grains and Upper Limits of "Restoration" for General Purpose Cereal Foods*

(Council on Foods and Nutrition, American Medical Association)

Product	Ca, Mg. per 100 Calories	Fe, Mg. per 100 Calories	Thia- mine, Mg. per 100 Calories	Ribo- flavin, Mg. per 100 Calories	Niacin, Mg. per 100 Calories
"Restored" cereal.....	75	1.5	0.25	0.10	
Cornmeal.....	7.2	0.9	0.005	0.05	0.4
Oatmeal.....	20	1.2	0.24	0.05	0.4
Whole wheat flour.....	14.8	1.4	0.13	0.07	1.8

been called the principle of restoration. Paragraph 4 of the statement of the National Research Council Committee is based on this idea of "restoration" of the milled product to something comparable to the natural one.

The following statement of the policy of the Federal Government with respect to the addition of nutritive ingredients to foods,^{6a} published July 3, 1943, is of interest in this connection:

The labeling or advertising of a food as enriched with vitamins and minerals is an implied promise to consumers that it contains, in addition to the normal constituents of the unenriched food, sufficient vitamins and minerals to make a substantial contribution to the nutritional welfare of persons eating the enriched food in customary amounts. In order to promote

6a. Federal Security Agency, Food and Drug Administration. Statement of Policy with respect to the addition of nutritive ingredients to foods, Federal Register 8:9170 (July 3) 1943.

honesty and fair dealing by fulfilling this implied promise, it is necessary that the kinds and quantities of enriching ingredients be determined in the light of deficiencies of the various nutritional factors in the diets of the population in general and of significant population groups, the place occupied by the food in such diets, and the suitability and effectiveness of the food as a carrier of the enriching ingredients without undue separation or loss before consumption.

Honesty and fair dealing will best be promoted if such enriched foods as are made available to consumers serve to correct such deficiencies and furnish a reasonable margin of safety. Enrichment above the levels required to accomplish this end is wasteful and contrary to the interest of most consumers; nutrient factors in concentrated form are available for use in those special cases of deficiencies in the diets of persons who do not constitute significant population groups. Enrichment of foods with nutrients that are supplied in adequate quantities by the diets of all significant population groups is not only wasteful but tends to confuse consumers as to their nutritional needs.

Knowledge of the roles in human nutrition of various components of food, particularly the vitamins, is incomplete. There is reason to believe that as new information is developed food factors not now recognized as essential may be shown to be necessary to adequate nutrition.

Most natural foods contain a wide variety of needed factors in significant amounts. It is highly probable that a diet of unenriched foods so chosen as to contain the required quantities of the presently known needed vitamins and other factors would more nearly supply all needed factors, known and unknown, than a diet which is raised by enrichment to adequacy in the vitamins and minerals now known to be needed.

Even though adequate nutrition could be better assured through the choice of natural foods than through reliance on enrichment, unenriched foods of the kinds and in the quantities necessary for adequate nutrition are not now available to substantial parts of the population and are not likely to be available soon; nor are most consumers sufficiently educated on nutritional questions to enable them to make an intelligent choice of combinations of unenriched foods on the basis of nutritional values.

Because of the lack of adequate production of a number of foods high in certain nutrients and the lack of consumer knowledge of nutrition, appropriate enrichment of a few foods widely consumed by the population in general or by significant population groups will contribute substantially to the nutritional welfare of consumers and to meeting their expectations of benefit. Enrichment of those foods which are not a substantial part of the dietary of any significant group tends to confuse and mislead consumers through giving rise to con-

flicting claims of nutritional values and by creating an exaggerated impression of the benefits to be derived from the consumption of such foods.

If the customary process of manufacturing a staple food refines it so as to remove significant quantities of nutritive factors present in the natural product from which the food is made, and if the refined food is a suitable and efficient carrier of the factors so removed, some nutritionists advocate the restoration of such factors to the levels of the natural product as the most desirable basis of enrichment. To the extent that restoration serves to correct deficiencies of such factors, it is consistent with the promotion of honesty and fair dealing that refined foods be enriched on a restoration basis. However, when the evidence shows that the restoration levels are too low to correct deficiencies, or that deficiencies exist in other factors for which the refined food is an efficient carrier, the promotion of honesty and fair dealing may require the inclusion of corrective quantities of nutritive factors in the enriched food even though such factors are present in smaller quantities or wholly lacking in the natural product from which the food is made. Similar considerations may require the enrichment of unrefined foods.

When a single dietary factor is being considered, this principle has much to commend it. For example, the processing of a fruit juice may result in appreciable loss of vitamin C, and products of this sort are normally very valuable as sources of this factor. The addition of ascorbic acid in amount sufficient to "restore" this particular processed juice to approximately the highest concentration characteristic of the natural juice would seem justifiable. The principle of restoration proves to be unsatisfactory, however, when the addition of more than one factor is being considered. In the case of ordinary wheat flour, for example, the addition of vitamin B₁ in amount sufficient to make the flour approximately equal to whole wheat with highest natural concentration means a significant addition of the restorative sort; a restorative addition of riboflavin (vitamin B₂) to the flour, however, means very little because the cereal grains are not good natural sources of this factor. If, therefore, riboflavin is nevertheless to be added to the flour in significant amounts, the addition means "fortification," because the enriched product will contain even more riboflavin than is found in the natural whole grain. It will be noticed in the statement of governmental policy quoted above, that this point is discussed.

When several dietary factors are being added to a given staple food, some in accordance with the principle of restoration, others in accordance with fortification, one is not limiting oneself to making the staple processed food as nearly as possible like the natural source but frankly modifying it to make an entirely new product to meet a particular nutritive situation. Enriched flour is the prime example of this. In such a case it is evident that the proposed addition of several factors is best made in some relation to the human requirement for them, taking into account the other sources of supply available in the dietary and other pertinent considerations. It may be questioned whether there are very many staple foods that lend themselves as suitable vehicles for the wider distribution and intake of several dietary factors instead of only one or perhaps two. In view of this there may still be a place for operation of the principle of restoration in the improvement of numerous processed foods.

OTHER METHODS OF IMPROVING FOODS

The foregoing discussion has dealt with the ideas that have been advanced for improving staple foods by what might be called the artificial addition of dietary factors lost as a part of food processing. There are other ways of achieving the same objective that should be mentioned. One may select plant varieties on the basis of genetic constitution and vitamin content. It is known that varieties of wheat and other cereals differ considerably in their respective contents of thiamine. Data bearing on this topic have been summarized by Taylor⁷ and are shown in table 3. In addition to illustrating the variation in thiamine content characteristic of cereal grains the data in table 3 emphasize a point frequently forgotten by those who argue that enrichment of flour is unnecessary, that the use of whole grain flour is the answer to the basic problem being attacked. There is no such thing as a standard whole wheat flour with respect to "high natural level" of thiamine content. The adoption and wide use of a standardized enriched flour in contrast to a nondescript unstandardized whole wheat product has therefore some definite points in its favor.

7. Taylor, A. E.: *Why Enrichment of Flour? Wheat Studies of the Food Research Institute, Stanford University* 18:77-108 (Nov.) 1941. See particularly page 92.

Some staple foods of plant origin can be nutritively improved by the adoption of special methods of cultivation. At the present time we do not know all that we should like to know about the effects of various environmental factors on the vitamin and mineral content of important plants that we use as food. The subject is being actively investigated.⁸ Exposure to sunlight, supply of special materials in the soil, water supply and similar factors require investigation. A food like the potato, which remains in the soil until harvested, is known to reflect in its iodine content the iodine concentration of the soil and water.⁹ In an iodine survey of various sections of the state of South Carolina the

TABLE 3.—*Thiamine Content of Cercal Grains and Types of Wheat*

Milligrams per Pound *

Kind of Grain	Thiamine	Type of Wheat	Thiamine
Oats.....	2.20-4.90	Durum.....	2.10-3.80
Wheat.....	1.45-3.80	Hard spring.....	1.45-3.49
Barley.....	2.58-3.33	Hard winter.....	1.08-2.71
Corn.....	1.85-3.04	Pacific.....	1.70-2.44
Rye.....	1.88-2.28	Soft red.....	1.70-2.38

* Original data from Taylor,⁷ who comments as follows: "These include analyses of pure varieties and nondescripts (more than random samples), commercial grades and ungraded, from good and poor crops, stored for short and longer periods, with different methods of assay. The significance spreads cannot be as wide as those given."

iodine content of potatoes grown in the respective areas proved to be as good a criterion of iodine supply as analyses of water and soil. In dealing with a shortage of dietary iodine, obviously, then, one has several possibilities, namely (a) wider use of sea food, which is an excellent natural source of this element, (b) wide use of a root vegetable like the potato cultivated in an iodine

8. Hamner, K. C.; Lyon, C. B.; Ellis, G. H., and Beeson, K. C.: Factors Influencing the Nutritive Value of the Tomato, Proc. Am. Inst. Nutrition, 9th Annual Meeting, Federation Proceedings, Part II, No. 1, March 16, 1942, p. 189. Rose, Mary S., and Phipard, Esther H. F.: Vitamin B and G Values of Peas and Lima Beans Under Various Conditions, J. Nutrition 14: 55-67 (July) 1937. Bonner, J., and Greene, J.: Vitamin B₁ and the Growth of Green Plants, Bot. Gaz. 100: 226-237, 1938. Lilly, V. G., and Leonian, L. H.: Vitamin B₁ in Soil, Science 89: 292 (March 31) 1939. Burkholder, P. R., and McVeigh, Ilda: Studies on Thiamine in Green Plants with the Phycomyces Assay Method, Am. J. Bot. 27: 853-861, 1940; Pyridoxine as a Growth Factor for Graphium, Science 85: 127-128 (Jan. 30) 1942.

9. Hayne, James A.: Endemic Goiter and Its Relation to Iodine Content of Food, Am. J. Pub. Health 19: 1111-1118 (Oct.) 1929.

enriched soil or water or (c) the fortification with iodine of a product such as table salt. The first two of these possibilities are impracticable for an inland area for obvious reasons yet valuable procedures in coastal regions; the inland area situation is more easily met by the use of iodized table salt.

Nutritive improvement of foods of animal origin like milk and its derivatives can be achieved in accordance with much the same principles. Milk is such a valuable food that nutritive improvement of it has not had very extensive consideration. Most of the discussion of this topic has centered around the use of fortified milk as a means of increasing the supply of vitamin D to growing children and thus improving the utilization of its calcium. Vitamin D milk may be obtained by direct addition to the milk of the vitamin, or a concentrate of it, with such products differing merely in the material added; such a milk is obviously a "fortified" one. Vitamin D may also be added to the milk through the metabolism of the cow by feeding a product like irradiated yeast, which contains the vitamin, or even the vitamin itself. This amounts to affecting the environment in which the milk is produced.

The addition of vitamin A to milk or its fat derivative butter has received some attention. The vitamin A content of butter is known to vary with the season, being low in winter and high in summer.¹⁰ The development of a butter more uniform in vitamin A content is a worthy objective of the butter industry that has apparently had less attention than it deserves; such a product would be the logical one with which to meet the competition offered by vitaminized oleomargarine. Vitamin A concentrates could of course be added to winter butter. In view of recent experiments by Deuel and his associates,¹¹ there is presented the possibility of significantly enriching cow's milk with vitamin A by feeding certain extremely concentrated preparations of the vitamin. Improved feeding of cows during the winter season constitutes another approach to solution of this question.

From this brief discussion it should be evident that by improving the quality of cheap staple foods it is

10. Dornbush, A. C.; Peterson, W. H., and Olson, F. R.: The Carotene and Vitamin A Content of Market Milks, *J. A. M. A.* **114**: 1748 (May 4) 1940.

11. Deuel, H. J., Jr.; Halliday, Nellie; Hallman, Lois F.; Johnston, Cornelia, and Miller, A. J.: The Production of High Vitamin A Milk by Diet, *J. Nutrition* **22**: 303 (Sept.) 1941.

possible to affect the public health in many important ways. The success which attends this method will obviously depend on several factors. One is the extent to which the consumer is made aware of the values of the improved product when it is in the market competing with the older unimproved but accepted food. The solution of this problem lies in consumer education, and in this work the physician can do much because of his influential position in the community. If the improved product can be given a favored status of some sort, its use will of course be increased. South Carolina and Louisiana have passed laws requiring all white flour sold in their respective domains to be of the enriched variety; and considerable attention is being given in many quarters to the enrichment of corn meal particularly with niacin as a means of combatting pellagra. Louisiana has also passed a law requiring that all oleomargarine offered for sale contain vitamin A. It is possible that still other states will follow the lead of South Carolina and Louisiana in these respects. This way of achieving greater consumption of a desired product has certain shortcomings as well as advantages. In the case of enriched flour used in these Southern states the advantages are believed greatly to outweigh the disadvantages, because in enriching its flour the milling industry has tended to enrich only the more expensive brands; it is especially important that the enriched flour be used extensively by the lower income groups of the population who have the least money to pay for the improved product. It is to the credit of the milling industry that it has sought to bring about by voluntary means the enrichment of all its staple flour by every unit of the industry. The enactment of laws to solve problems always poses of course some additional problems of effective enforcement and the like; whether a law will be readily accepted, no matter how desirable it may be from a strictly scientific point of view, depends on a sufficient number of the people being properly informed and convinced of its value. Thus we are brought around once more to the fact that the fundamental solution of our basic problem lies in effective education of the general public with respect to the principles of nutrition, food values and related topics. Given the proper education in these matters, the general public will naturally prefer more and more the improved

staple foods over those that are not improved; the extent to which this occurs will very largely determine the role that this particular application of modern knowledge in nutrition plays in promoting the public health.

CHAPTER XVII

RECOMMENDED DIETARY ALLOWANCES

FOOD AND NUTRITION BOARD, NATIONAL RESEARCH COUNCIL

Dietary standards to serve as a goal for good nutrition and as a "yardstick" by which to measure progress toward that goal have long been needed. In 1935 the League of Nations made a concerted group effort to formulate such a yardstick. One of the first concerns of the Food and Nutrition Board (formerly the Committee on Food and Nutrition of the National Research Council), established in 1940 to advise on nutrition problems in connection with National Defense, was to define in accordance with newer information the recommended daily allowances for the various dietary essentials for people of different ages.

The difficulty in such an undertaking lies in the lack of sufficient experimental evidence on which to estimate requirements for the various nutrients with any great degree of accuracy. Judgments as to requirements are necessarily based on incomplete and often conflicting reports of research and clinical observations and on data derived from work on animals. Experiments with the various vitamins also differ with regard to procedure and interpretation. These variables explain the wide divergence in "requirements" as set forth in current literature on nutrition.

In view of the confusion caused by this great variation in standards used, it seemed desirable to attempt to derive a table of allowances which would represent the best available evidence on the amounts of the various nutritive essentials to include in practical diets. With this aim in view, the literature on the subject of each of the dietary essentials was critically appraised, and in addition judgments as to the various requirements were solicited from a considerable number of nutrition authorities in addition to members of the Board, especially those whose research bore particularly on the problem.

On the basis of this evidence tentative allowances were formulated. These were resubmitted to contributors for criticism and reformulated in the light of the comments made. The values thus revised were presented before a section meeting of the American Institute of Nutrition in 1941 and members invited to submit further evidence for any changes that seemed indicated. After final discussion and some minor revisions they were adopted by the Board in May 1941. The values as presented thus represented the combined judgment of more than fifty persons qualified to express an opinion on the subject. This does not mean, of course, that every contributor would fully agree with all the figures as given. It does mean, however, that the values are ones they were willing to accept tentatively, until standards derived from more extensive and exact research data can be obtained. The term "Recommended Allowances" rather than "Standards" was adopted by the Board to avoid any implication of finality.

In using these recommendations, it is important that the purpose and general policies in formulating them should be understood:

WHAT THE ALLOWANCES PROVIDE

The allowances for specific nutrients are intended to serve as a guide for planning adequate nutrition for the civilian population of the United States. The quantities given were planned to provide not merely the minima sufficient to protect against actual deficiency disease but a fair margin above this to insure good nutrition and protection of all body tissues. Since the actual requirements for these purposes are not known it is recognized that the margins of safety may vary considerably for the different factors. The Board realizes that the values proposed will need to be revised from time to time as more knowledge of nutritive requirements becomes available.

NO ALLOWANCES FOR LOSSES IN COOKING

It should be pointed out that the vitamin figures are calculated requirements for food as eaten and do not allow for losses in cooking. Since such losses may be extensive, especially of the water-soluble vitamins, provision should be made for them in planning practical dietaries.

TABLE 1.—*Recommended Dietary Allowances**
Food and Nutrition Board, National Research Council

	Calories	Protein, Gm.	Calcium, Gm.	Iron, Mg.	Vitamin A,** I. U.	Thiamin (B ₁), Mg.**	Ribo- flavin, Mg.	Niacin (Nicoti- nic Acid), Mg.	Ascorbic Acid,** Mg.	Vitamin D, I. U.
Man (70 Kg.)										
Sedentary.....	2,500				1.5	2.2	15		
Moderately active.....	3,000	70	0.8	12	5,000	1.5	2.7	18	75	†††
Very active.....	4,500	2.3	3.3	23
Woman (56 Kg.)										
Sedentary.....	2,100				1.2	1.8	12		
Moderately active.....	2,500	60	0.8	12	5,000	1.5	2.2	15	70	†††
Very active.....	3,000	1.8	2.7	18
Pregnancy (latter half).....	2,500	85	1.5	15	6,000	1.8	2.5	18	100	400 to 800
Lactation.....	3,000	100	2.0	15	8,000	2.3	3.0	23	150	400 to 800
Children up to 12 years:										
Under 1 year †.....	100/Kg. 3 to 4/Kg.		1.0	6	1,500	0.4	0.6	4	80	400 to 800
1-3 years †.....	1,200	40	1.0	7	2,000	0.6	0.9	6	85	†††
4-6 years.....	1,600	50	1.0	8	2,500	0.8	1.2	8	50	...
7-9 years.....	2,000	60	1.0	10	3,500	1.0	1.3	10	60	...
10-12 years.....	2,500	70	1.2	12	4,500	1.2	1.5	12	75	...
Children over 12 years:										
Girls, 12-15 years.....	2,800	80	1.3	15	5,000	1.4	2.0	14	80	†††
16-20 years.....	2,400	75	1.0	15	5,000	1.2	1.8	12	80	...
Boys, 12-15 years.....	3,200	85	1.4	15	5,000	1.6	2.4	16	90	†††
16-20 years.....	3,800	100	1.4	15	6,000	2.0	3.0	20	100	...

* Tentative goal toward which to aim in planning practical diets; can be met by a good diet of natural foods. Such a diet will also provide other minerals and vitamins, the requirements for which are less well known.

** 1 mg. thiamin equals 333 I. U.; 1 mg. ascorbic acid equals 20 I. U.

†† Requirements may be less if provided as vitamin A; greater if provided chiefly as the provitamin carotene.

† Needs of infants increase from month to month. The amounts given are for approximately 6-8 months. The amounts of protein and calcium needed are less if derived from human milk.

†† Allowances are based on needs for the middle year in each group (as 2, 5, 8, etc.) and for moderate activity.

††† Vitamin D is undoubtedly necessary for older children and adults. When not available from sunshine, it should be provided probably up to the minimum amounts recommended for infants.

Further Recommendations, Adopted 1942:

The requirement for iodine is small; probably about 0.002 to 0.004 milligram a day for each kilogram of body weight. This amount is about 0.15 to 0.30 milligram daily for the adult. This need is easily met by the regular use of iodized salt; its use is especially important in adolescence and pregnancy.

The requirement for copper for adults is in the neighborhood of 1.0 to 2.0 milligrams a day. Infants and children require approximately 0.05 per kilogram of body weight. The requirement for copper is approximately one tenth of that for iron.

The requirement for vitamin K is usually satisfied by any good diet. Special consideration needs to be given to newborn infants. Physicians commonly give vitamin K either to the mother before delivery or to the infant immediately after birth.

OTHER FACTORS FOR WHICH ALLOWANCES
ARE NOT GIVEN

In addition to the three factors of the B complex included, other members of the group, such as vitamin B₆ and pantothenic acid, should be given consideration. But at the present time no specific values can be given for the amount required in the human dietary. It should be added, however, that foods supplying an adequate amount of thiamin, riboflavin, and niacin (nicotinic acid) will tend to supply an adequate amount of the remaining B vitamins. Similarly diets providing adequate amounts of protein, calcium and iron will tend to supply other needed minerals, though these are not listed. There is urgent need for continued research on the requirements for all dietary essentials, especially for children.

ALLOWANCES BASED ON AVERAGE SIZE, SEX AND
ACTIVITY FOR NORMAL INDIVIDUALS

The allowances for adults are given for the 70 Kg. man and the 56 Kg. woman at three levels of activity. They will need to be proportionately increased or decreased for larger or smaller individuals. It will be noted that the allowances for thiamin, riboflavin and niacin (nicotinic acid) are proportional to the caloric intake. This relationship has been established for thiamin, and it has been assumed to hold also for riboflavin and nicotinic acid since, like thiamin, they are part of the enzymic system involved in the metabolism of carbohydrate.

The allowances for children are given by age groups, and for boys and girls separately after 12 years, since from that age the growth curves and levels of activity for the two sexes differ. The values presented are in each case for the middle year in the group, and represent amounts needed for children of average size and activity. The needs for individual children may be proportionately larger or smaller depending upon size and activity.

It is to be understood that these allowances are for persons in health, and that needs may vary markedly in disease. For example, in febrile conditions there is usually an increased need for calories, thiamin and ascorbic acid. The need for these or other constituents

may also be greatly altered in other diseases, especially those of the alimentary tract, which interfere with normal absorption.

SLIGHT CHANGES IN 1941 ALLOWANCES

Recommendations as adopted in 1941 remain substantially unchanged at this writing—approximately two years after the initial compilation of data.

Consideration has been given to three more nutrients not covered in the original recommendations. They are iodine, copper and vitamin K. Recommendations for these substances are now included for the first time in this summary.

DIET PLANS THAT MEET THE DIETARY ALLOWANCES

In using the recommended allowances it should be emphasized that the amounts of the various nutrients provided for in these recommended allowances, with the exception of vitamin D can be obtained through a good diet of natural foods including foods like enriched white flour and bread which have been improved according to recommendations of the Board.

The safest way to insure that the dietary allowances are met is to include certain foods in the diet daily in specified amounts. One dietary pattern which contains a variety of foods commonly available is given below:

List I

Milk	1 pint
Egg	1 daily, if possible. (On days not used, beans, peanuts, cheese, or more milk or meat to be used instead)
Meat, fish or fowl.....	1 or more servings
Potato	1 or more
Vegetables	2 or more servings. One green or yellow
Fruits ..	2 or more. One citrus fruit or tomato or other good source of vitamin C
Cereals and bread.....	Whole-grain or enriched
Other foods as needed to complete the meals	

This list is based on the needs of the average adult. For children the milk needs to be increased but the kinds of foods to include remain the same.

Another list using less milk and lean meat is given as illustrative of the varied ways in which the allowances may be met.

List II

Turnip greens	1 cup
Sweet potatoes	3
Peanuts	20 nuts or 2 tablespoons of peanut butter
Beans or cowpeas.....	1½ oz.
Tomatoes	1 cup
Corn meal	3 oz.
Enriched flour	3 to 4 oz.
Milk (fresh, evaporated or dried)	⅓ pt.
Lean pork	small serving 3 to 4 times a week
Molasses, fat, etc., to complete the meals	

Calculations show that both these lists meet the dietary allowances. It should be pointed out, however, that every food is needed in the amounts specified. If any food is omitted, therefore, it should be replaced by another of equal value.

There are many other combinations of foods that will also cover these allowances. It is expected that nutrition workers in various parts of the country will translate these allowances into appropriate quantities of foodstuffs available in their localities and suited to the income level of the group concerned. Such allowances, expressed in terms of everyday foods, can then be widely used in practical nutrition work.

CHAPTER XVIII

THE FEEDING OF HEALTHY INFANTS AND CHILDREN

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THE FEEDING OF INFANTS

Human milk commonly is considered the ideal food for the young infant, presumably supplying all nutritional essentials for the early period with the exception of adequate vitamin D. When human milk is not available, cow's milk is the material most commonly used in substitution. It seems desirable to review the comparisons of these two foods as to their contents of various nutritional essentials and their effects on the growth and body composition of the infant. Comparative contents of the two milks are shown in tables 1 and 2.

The protein requirement of the infant commonly is stated on the basis of the average amount received in human milk when he is making good growth progress. The amount of protein received by the young infant under these circumstances is 2 to 2.5 Gm. for each kilogram of body weight. Acceptance of the concept, not clearly proved, that human milk protein is biologically superior to cow's milk protein by a factor approximating 20 per cent makes the requirement of the young infant for cow's milk protein 2.5 to 3 Gm. for each kilogram. It is a common practice to supply the young artificially fed infant with at least 1½ ounces of milk for each pound of body weight. This amount is equivalent to 100 cc. for each kilogram and a protein intake of 3.4 Gm. for each kilogram, an amount in excess of the theoretical requirement as based on the assumed requirement for human milk. Many pediatricians prescribe even larger quantities of milk.

Observations have been made on the effect of ingestion of the larger quantities of cow's milk in comparison with the effects of feeding human milk. In chart 1 are shown the percentages of nitrogen content of infants when they are given these two types of food. After

TABLE 1.—*Approximate Percentage Composition of Human Milk and Cow's Milk*

	Fat	Sugar	Total Protein	Lact- albumin	Casein	Total Ash	Ca	Mg	K	Na	P	S	Cl	Fe	Cu
Human milk.....	3.5	7.5	1.25	0.75	0.50	0.20	0.034	0.005	0.048	0.011	0.015	0.0036	0.036	0.0001	0.00003
Cow's milk.....	3.5	4.7	3.4	0.50	3.0	0.75	0.122	0.013	0.154	0.060	0.090	0.081	0.116	0.00004	0.00002

From Marriott, W. M.: Infant Nutrition, revised by P. C. Jeans, St. Louis, C. V. Mosby Company, 1941.

birth the percentage of nitrogen content of babies receiving cow's milk increases in a curve smoothly continuous with the curve of prenatal content¹ and in a manner comparable to the curve predicted by Moulton² for the fat free animal body. On the other hand, when human milk is fed, a sharp change in direction of the curve of percentage composition occurs after birth and for a time the proportion of nitrogen in the body remains at the birth level or decreases slightly.¹

Somewhat similarly to the body content of nitrogen, the percentage calcium content of the body differs after

TABLE 2.—*Approximate Vitamin Content of Human and Cow's Milk*

Values for Each Hundred Grams or Cubic Centimeters

	Total A, I. U.	D, I. U.	C, Mg.	Thiamine, Mg.	Riboflavin, Mg.	Niacin, Mg.
Human milk...	60-500	0.4-10	1.2-10.8	0.002-0.036	0.015-0.08	0.1
Average.....	250		6.4	0.013	0.04	
Cow's milk....	80-220	0.3-4.4	1.1-2.9	0.018-0.075	0.10-0.26	0.07-0.15
Average raw...	180		2.0	0.045	0.20	0.10
Past... ..	No loss	No loss	0.9-1.4	0.030-0.040	No loss	
Evap... ..						
Reconst.....	No loss	No loss	0.6	0.20*-0.030	No loss	

* After several months' storage.

N. B.: Pantothenic acid, cow's milk, average 0.25-0.40 mg. for each hundred cubic centimeters. (Elvehjem.¹⁷ Jukes, T. H.: The Distribution of Pantothenic Acid in Certain Products of Natural Origin, *J. Nutrition* 21:193-199 [Feb.] 1941). Pyridoxine, cow's milk, 0.13-0.20 mg. for each hundred cubic centimeters (Elvehjem.¹⁷ Henderson, LaVell M.; Walsman, H. A., and Elvehjem, C. A., *ibid* 21:589-598 [June] 1941); human milk content approximately the same as that of cow's milk (György, Paul: Quantitative Estimation of Lactoflavin and of Vitamin B₆ in Cow Milk and in Human Milk, *Proc. Soc. Exper. Biol. & Med.* 35:204-207 [Oct.] 1936). Biotin, cow's milk, average 0.001-0.004 mg. for each hundred cubic centimeters (Lampen, J. O.; Bahler, G. P., and Peterson, W. H.: *J. Nutrition* 23:11-21 [Jan.] 1942. Shull, G. M.; Hutchins, B. L. and Peterson, W. H.: A Microbiological Assay for Biotin, *J. Biol. Chem* 142:913-920 [Feb.] 1942).

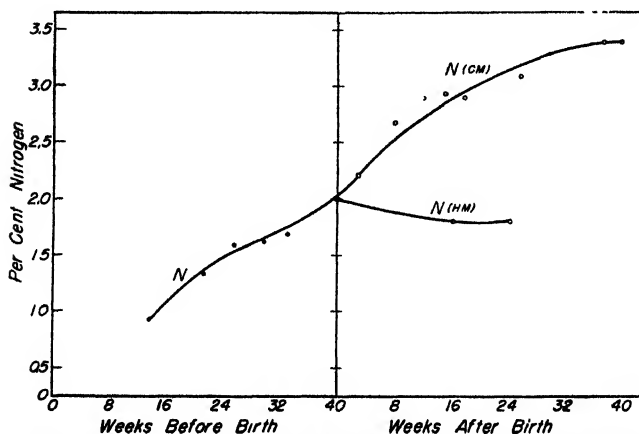
birth with human and cow's milk feeding.¹ As shown in chart 2, a decrease occurs with both types of feeding for several weeks after birth, after which period the body content with cow's milk feeding starts to rise, while that with human milk feeding continues to fall for several weeks more and probably does not reach the birth value before the baby is 1 year of age. The calcium of human milk is used more efficiently than that of cow's milk, but the total retention from cow's milk

1. Stearns, Genevieve: The Mineral Metabolism of Normal Infants, *Physiol. Rev.* 10:415-430 (July) 1939.

2. Moulton, C. R.: Age and Chemical Development in Mammals, *J. Biol. Chem.* 57:79 (Aug.) 1923.

is far greater because of the larger quantity fed. The calcium retention of the baby fed cow's milk is as great as or greater than the intake of the breast fed baby.

The significance of these various differences in body composition of the infant is not clear. One interpretation could be that a wide range of normal exists and that these differences are of no significant importance. The period of time during which these differences exist is relatively short compared with the life span. The differences disappear soon after the differences in diet cease to exist. While this point of view may be acceptable for the baby born at term, it seems inappropriate



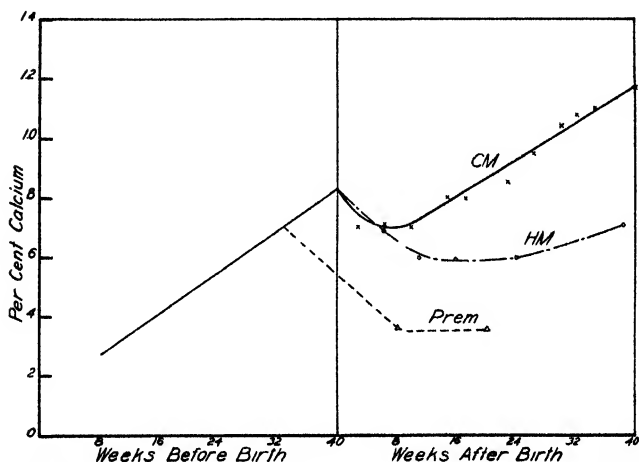
(Reproduced by permission from article by Genevieve Stearns "Mineral Metabolism of Normal Infants," *Physiol. Rev.* **19**: 415-430 [July] 1939.)

Chart 1.—Changes in relative nitrogen content of fetus and infant. The regression line of nitrogen content of the fetus is drawn from data in the literature. *C. M.*, infants fed cow's milk; *H. M.*, infants fed human milk (Redrawn from Stearns: Mineral Metabolism of Normal Infants.¹).

for the baby born prematurely, at least as concerns calcium. The chief reason the prematurely born baby is highly susceptible to rickets appears to be the low calcium content of the body at birth and the difficulty of supplying sufficient of this material after birth. Human milk cannot be ingested in sufficient amounts to supply the calcium need unless it is fortified or supplemented with calcium or a calcium containing food.

In explanation of the high calcium content of the baby fed cow's milk as compared with the baby fed

human milk, and perhaps with the justifiable concept that human milk is the ideal food, the idea has been advanced that the baby fed cow's milk is supermineralized. Eliot and Park³ interpreted the results of their study of the bones of newborn babies as indicating that calcium is present in sufficient amount to represent storage. This interpretation was accepted by Hamilton,⁴ who expressed the belief that the relative calcium loss in early infancy represents utilization of stores and is normal. After 3 months of age the rate of percentage of calcium increase in the body when cow's milk is fed



(Reproduced by permission from article by Genevieve Stearns "Mineral Metabolism of Normal Infants," *Physiol. Rev.* **19**: 415-430 [July] 1939.)

Chart 2.—Changes in relative calcium content of fetus and infant. The regression line of calcium content of fetus is drawn from data in the literature. *C. M.*, infants fed cow's milk; *H. M.*, infants fed human milk; *Prem.* prematurely born infants fed human milk. (From Stearns' by permission of Physiological Reviews, Inc.)

parallels the fetal rate, a condition which, if it does not represent physiologically normal growth, at least produces storage. Storage to this extent certainly is not harmful, and it may well be considered useful during periods of illness when calcium utilization is impaired. The rate of calcium increase after 3 months of age for

3. Eliot, Martha M., and Park, E. A.: *Rickets*, in Brennemann's *System of Pediatrics*, Hagerstown, Md., W. F. Prior Company, 1938, vol. 1, chapter 36.

4. Hamilton, B.: Calcium and Phosphorus Metabolism of Prematures, *Acta paediat.* **2**: 1-83, 1923.

the baby fed cow's milk is similar to the rate of increase of the ash content of the fat free animal body as predicted by Moulton.²

Linear growth of babies fed a standardized cow's milk formula is related to the amount of calcium retained.⁵ The differing retentions with the standardized diet are obtained by varying the vitamin D intake. Babies with poor retentions grow at average or less than average rates, while those with higher retentions grow at rates greater than average. Thus the higher calcium retentions would appear to be definitely advantageous to the artificially fed infant. On the other hand the breast fed baby has excellent linear growth despite the much lower calcium retention and grows at a definitely greater rate than the artificially fed baby with the same calcium retention.⁶ It becomes obvious from these and other facts that factors other than those under consideration enter into the rate of growth and that probably it is inappropriate to state requirement standards for the artificially fed baby based on the requirement of the baby fed human milk.

The greater nitrogen retention of the artificially fed baby must of necessity represent larger amounts of tissue protein in the body, since nitrogen is not stored in any other fashion. The larger part of the increase in tissue protein is represented in increase in muscle mass. Babies who are fed cow's milk in the larger of the customary quantities have approximately 25 per cent more muscle mass than babies breast fed.⁷ This increase takes place soon after artificial feeding is started, after which time the muscle mass maintains a fairly constant relationship to the total body weight. Thus the muscle masses of breast fed and artificially fed babies increase in a parallel manner, but with larger values for those receiving cow's milk. No disadvantage seems to accrue to the breast fed baby because of the lesser amount of muscle. On the other hand nitrogen retentions of the artificially fed baby of the same order of magnitude as those of the breast fed baby are associated with

5. Stearns, Genevieve; Jeans, P. C., and Vandecar, Verva: The Effect of Vitamin D on Linear Growth in Infancy, *J. Pediat.* **9**: 1-12 (July) 1936. Slyker, Francis; Hamil, B. M.; Poole, M. W.; Cooley, T. B., and Macy, Icie G.: Relationship Between Vitamin D Intake and Linear Growth in Infants, *Proc. Soc. Exper. Biol. & Med.* **27**: 499-502 (Dec.) 1937. Jeans and Stearns.¹⁰

6. Jeans, P. C., and Stearns, Genevieve: Unpublished data.

7. Catherwood, Ruth, and Stearns, Genevieve: Creatine and Creatinine Excretion in Infancy, *J. Biol. Chem.* **110**: 201-214 (June) 1937.

poorer tissue turgor and poorer motor development than are shown by artificially fed babies receiving the larger amounts of cow's milk and having higher nitrogen retentions. If these observations are correct, cow's milk formulas devised to simulate human milk in composition are not as useful as are formulas containing larger amounts of protein and calcium.

The phosphorus content of the body and the phosphorus requirement depend on the amounts of calcium and nitrogen retained. Consequently the requirement of the baby receiving cow's milk is somewhat greater than that of the infant fed human milk. The phosphorus content of human milk is much less than that of cow's milk, but human milk contains an amount sufficient to meet the needs of the infant relative to the amounts of nitrogen and calcium retained. Cow's milk contains an excess to the extent that much more phosphorus is absorbed than can be used, the excess being excreted chiefly in the urine. Little or no phosphorus is excreted in the urine of the breast fed baby, whereas in the artificially fed baby 60 to 70 per cent of the total excretion is by way of the urine. The baby seems to accomplish the increased excretion without difficulty or damage.

Human milk is superior to cow's milk as a source of iron. Though human milk contains only from 0.5 to 1.5 mg. of iron to the liter, it contains on the average three times as much as does cow's milk. The iron stores of the body of the baby at birth are sufficient to permit maintenance of a normal hemoglobin level for several months, after which time additional iron is necessary. After 3 months of age with customary cow's milk formulas the iron retention is variable, but averages approximately zero; when human milk is fed, the average retention is approximately 0.11 mg. Neither of these iron intakes is satisfactory, for a retention of at least 0.7 mg. is required after 6 months to maintain the hemoglobin level.⁸ Without additions the body of the baby becomes progressively poorer in iron. The iron content of human milk and its utilization are such that nutritional anemia is much slower to develop in the breast fed baby than in the artificially fed baby when no iron supplement is given.

8. Stearns, Genevieve, and Stinger, Dorothy: Iron Retention in Infancy, *J. Nutrition* **13**: 127-141 (Feb.) 1937.

Many times in the past the question has arisen whether the infant needs vitamin A in addition to that present in a customary diet and without the use of any of the fish liver oils. In the light of present knowledge of the requirement of the infant for vitamin A, the Food and Drug Administration has set the minimum requirement at 1,500 units daily and the Food and Nutrition Board of the National Research Council has recommended the same amount as a suitable allowance. For a baby 1 year old this amount is greater than that computed as optimum on the basis of weight from animal experiments when all the vitamin A is ingested as carotene. Thus the amount suggested appears to be ample even if supplied wholly by carotene. Computation shows that the required amount of vitamin A is supplied by milk alone, either human⁹ or bovine,¹⁰ if it is of average content. In the early months the breast fed baby receives more vitamin A than does the baby fed a cow's milk formula prepared by dilution. In addition to the vitamin A of the milk the early addition of orange juice makes a small contribution and the subsequent additions of egg yolk, vegetables and fruits permit an intake of vitamin A well above the requirement. Clinical observations also have shown that babies receiving a normal standard diet grow equally well whether or not they receive additional vitamin A in fish liver oil.¹¹ Thus for the average baby the important contribution of fish liver oil is vitamin D.

The ascorbic acid content of human milk varies directly with the intake of the mother¹² but in general is relatively large in comparison with the content of prepared cow's milk. An approximate average content of human milk in this country is 60 mg. to the quart,¹² whereas a cow's milk formula prepared by boiling and

9. Friderichsen, C., and With, T. K.: Ueber den Gehalt der Frauenmilch an Karotinoiden und A-Vitamin, besonders in bezug auf seine Abhängigkeit von der Kost, *Ann. paediat.* **153**: 113-143 (June) 1939. Dann, W. J.: The Transmission of Vitamin A from Parents to Young in Mammals: V. The Vitamin A and Carotenoid Contents of Human Colostrum and Milk, *Biochem. J.* **34**: 724-735 (May) 1940.

10. Dornbush, A. C.; Peterson, W. H., and Olson, F. R.: The Carotene and Vitamin A Content of Market Milks, *J. A. M. A.* **114**: 1748-1751 (May 9) 1940. *Tech. Bull.* 802, U. S. Dept. Agric., December, 1941.

11. Lewis, J. M., and Barenberg, L. H.: The Relationship of Vitamin A to the Health of Infants, *J. A. M. A.* **110**: 1338-1341 (April 23) 1938. Jeans and Stearns.²⁶

12. Selleg, Iva, and King, C. G.: The Vitamin C Content of Human Milk and Its Variation with Diet, *J. Nutrition* **11**: 599-606 (June) 1936. Winkler, H., and Heins, E.: Der Askorbinsäuregehalt der Frauenmilch im Sommer und Winter, *Ztschr. f. Geburtsh. u. Gynäk.* **117**: 148-164, 1938.

dilution may contain 6 mg. or less to the day's supply.¹³ Thus average human milk meets the present standard allowance for vitamin C, whereas the amount in prepared cow's milk is grossly inadequate. Even though the requirement is met by average human milk, the feeding of orange juice to the breast fed baby is in no way harmful and may be considered beneficial in those instances in which the mother's supply of this material is small.

The thiamine content of human milk varies widely and depends on the diet of the mother.¹⁴ According to Knott and her co-workers,¹⁵ milk from mothers able to supply their infants adequately contains more thiamine than milk from mothers whose babies require a formula supplement. The milk of the mothers of babies requiring supplement contained an average of 86 micrograms (29 units) to the quart. When the milk supply of the mother was adequate, the average thiamine content of the milk was 192 micrograms (64 units) to the quart. The larger of these two thiamine contents was observed when the intake of the mothers was approximately 1.5 mg. of thiamine daily. When the two groups of mothers were considered together, the average thiamine content of the milk was 144 micrograms (48 units) to the quart. Clements¹⁶ observed

13. Holmes, A. D.; Tripp, Francis; Woelffer, E. A., and Satterfield, G. H.: Ascorbic Acid Content of Cow's Milk at Various Stages of Lactation, *Am. J. Dis. Child* **60**:1025-1030 (Nov.) 1940. Riddell, W. H.; Whitnah, C. H.; Hughes, J. S., and Lienhardt, H. F.: Influence of the Ration on the Vitamin C Content of Milk, *J. Nutrition* **11**:47-54 (Jan.) 1936. Hawley, Estelle E.: Vitamin C Content of Milks: Raw, Pasteurized and Baby Formulae, *J. Am. Dietet. A.* **14**:275-277 (April) 1938. Trout, G. M., and Gjessing, E. C.: Ascorbic Acid and Oxidized Flavor in Milk: I. Distribution of Ascorbic Acid and Occurrence of Oxidized Flavor in Commercial Grade A Raw, in Pasteurized Irradiated, and in Pasteurized Milk Throughout the Year, *J. Dairy Sc.* **22**:271-281, 1939. Holmes, A. D.; Tripp, Francis; Woelffer, E. A., and Satterfield, G. H.: The Influence of Pasteurization on the Ascorbic Acid (Vitamin C) Content of Certified Milk, *J. Am. Dietet. A.* **15**:363-368 (May) 1939. Rasmussen, Russel; Guerrant, N. B.; Shaw, A. O.; Welch, R. C., and Bechdel, S. I.: Effects of Breed Characteristics and Stages of Lactation on the Vitamin C (Ascorbic Acid) Content of Cow Milk, *J. Nutrition* **11**:425-432 (May) 1936.

14. Morgan, Agnes F., and Haynes, Edna G.: Vitamin B₁ Content of Human Milk as Affected by Ingestion of Thiamine Chloride, *J. Nutrition* **18**:105-114 (Aug.) 1939. Slater, E. C., and Rial, E. J.: The Thiamine (Vitamin B₁) in Human Milk, *M. J. Australia* **1**:3-12 (Jan. 3) 1942. Widenbauer, F., and Heckler, F.: Ueber den Vitamin B₁-Gehalt der Kuh- und Frauenmilch, *Ztschr. f. Kinderh.* **60**:683-690, 1939. Kendall, Norman: Thiamine Content of Various Milks, *J. Pediat.* **20**:65-73 (Jan.) 1942. Knott, Kleiger and Bracamonte.¹⁵

15. Knott, Elizabeth M.; Kleiger, Sarah C., and Bracamonte, F. T.: Factors Affecting the Thiamine Content of Breast Milk, *J. Nutrition* **25**:49 (Jan.) 1943.

16. Clements, F. W.: The Symptoms of Partial Vitamin B₁ Deficiency in Breast Fed Infants, *M. J. Australia* **1**:12-16 (Jan. 3) 1942.

symptoms of partial thiamine deficiency in 8 per cent of a group of 150 breast fed infants. The thiamine content of the milk was low in each case.

Cow's milk as fed to babies is subjected to heat treatment, which causes significant losses of thiamine as compared to the original milk. Data concerning the proportion of loss are few and not wholly in agreement.¹⁷ Reference to the values shown in table 2 shows that heat treated cow's milk contains more thiamine than does human milk. However, cow's milk usually is diluted for feeding the young baby. Even with maximum customary dilution, the thiamine intake of the artificially fed baby equals or exceeds that of the breast fed baby when averages are considered.

The Food and Nutrition Board of the National Research Council has set a standard allowance for thiamine at 0.4 mg. (133 units) for infancy, the Food and Drug Administration a minimum requirement at 0.25 mg. (83 units). These values may be interpreted to indicate a requirement of 40 and 25 micrograms respectively for each kilogram of body weight. Knott has stated a probable requirement of 40 micrograms for each kilogram.¹⁸ Though these standards are approached, only the Food and Drug Administration standard is fully attained by average human milk or by the average formula. It is by reason of these facts that questions have arisen as to the adequacy of the thiamine intake of the infant, particularly the breast fed infant. The breast fed infant, though he has no thiamine to spare, seems to do very well nutritionally. One difference between human milk and formulas of cow's milk is the higher proportion of calories from fat in human milk feeding. Slightly more than 50 per cent of the calories of human milk are from fat, while the calories from fat in a customary milk formula often are as low as 35 per cent. Thiamine is not concerned

17. Elvehjem, C. A.: *Meat and Human Health*, J. Am. Dietet. A. 18: 145-148 (March) 1942; *The Water Soluble Vitamins*, J. A. M. A., to be published. Boas-Fixsen, Margaret A., and Roscoe, Margaret H.: *Tables of the Vitamin Content of Human and Animal Foods*, Nutrition Abstr. & Rev. 7: 823-867 (April) 1938. Halliday, Nellie, and Dueul, H. J., Jr.: *The Presence of Free and Combined Thiamine in Milk*, J. Biol. Chem. 140: 555-561 (Aug.) 1941. Clouse, Ruth C.: *Essentials of an Adequate Diet*: II. Hygeia 19: 727-729 (Sept.) 1941. Tech. Bull. 707, U. S. Dept. Agric., December, 1939. Schlutz, F. W., and Knott, Elizabeth M.: *Factors Affecting the Vitamin B₁ Content of Evaporated Milk*, Proc. Soc. Exper. Biol. & Med. 40: 532-535 (April) 1939. Slater and Rail.¹⁴ Widenbauer and Heckler.¹⁴

18. Knott, Elizabeth M.; Kleiger, Sarah C., and Schlutz, F. W.: *Is Breast Milk Adequate in Meeting the Thiamine Requirement of Infants?* J. Pediat., to be published.

in fat metabolism, and fat consequently has a sparing action on this material. Therefore the thiamine requirement is more equally met in the two instances than seems apparent at first thought. In any case early supplement with thiamine containing foods is desirable.¹⁸

The riboflavin content of milk varies widely for the human being¹⁹ and to a lesser extent for the cow,²⁰ depending on the intake. The average content of cow's milk is approximately five times that of human milk, and the baby's supply from human milk probably reaches only occasionally the minimum standard of 0.5 mg. daily set by the Food and Drug Administration or 0.6 mg. recommended by the Food and Nutrition Board. However, human milk comes much nearer to meeting the stated requirement for riboflavin than it does for thiamine. Applying the same type of discussion as was given for thiamine, it would appear that the average breast fed baby probably is adequately supplied with riboflavin.

Both human and cow's milk are poor sources of nicotinic acid or niacin,²¹ human milk probably being the poorer of the two as with most other members of the vitamin B complex. It is probable that the amount of niacin in milk, at least human milk, is dependent on the intake of the mother. On the basis that the requirement for niacin is approximately ten times that for thiamine, the niacin requirement of the infant may be from 250 to 400 micrograms for each kilogram. Thus the requirement of the young infant, before niacin containing supplements are commonly given, would be from 1 to 2 mg. daily. If such a requirement is met, it is only barely met by either human milk or formulas

19. Neuweiler, W.: Ueber den Flavinegehalt der Frauenmilch, *Klin. Wchnschr.* **16**: 1348-1350 (Sept. 25) 1937. Müller, Rudolf: Beobachtung über dem Lacto-flavinegehalt der Frauenmilch und seine Beeinflussung durch die Ernährung, *Klin. Wchnschr.* **16**: 807-810 (June 5) 1937.

20. Henry, K. M.; Houston, J., and Kon, S. K.: Estimation of Riboflavin: Part 2. The Estimation of Riboflavin in Milk: Comparison of Fluometric and Biological Tests, *Biochem. J.* **34**: 607-624 (April) 1940. Johnson, P.; Maynard, L. A., and Loosli, J. K.: The Riboflavin Content of Milk as Influenced by Diet, *J. Dairy Sc.* **24**: 57-64, 1941. Clouse, Ruth C.: Essentials of an Adequate Diet: III. Hygeia **19**: 817-818 (Oct.) 1941. Elvehjem.¹⁷

21. Kodicek, E.: Estimation of Nicotinic Acid in Animal Tissues, Blood and Certain Foodstuffs: 2. Applications, *Biochem. J.* **34**: 724-735 (May) 1940. Teply, L. J.; Strong, F. M., and Elvehjem, C. A.: The Distribution of Nicotinic Acid in Foods, *J. Nutrition* **28**: 417-423 (April) 1942. Bailey, E. A., Jr.; Dann, W. J.; Satterfield, G. H., and Grinnells, C. D.: A Method for the Estimation of Nicotinic Acid in Milk, *J. Dairy Sc.* **24**: 1047-1053, 1941. Noll, C. I., and Jensen, O. G.: The Chemical Determination of Nicotinic Acid in Milk, *J. Biol. Chem.* **140**: 755-762 (Sept.) 1941. Snell, E. E., and Wright, L. D.: A Microbiological Method for the Determination of Nicotinic Acid, *ibid.* **139**: 675-686 (June) 1941.

of cow's milk. In the present state of our knowledge early supplement with niacin containing foods seems desirable for all infants.

Neither human ²² nor cow's milk ²³ supplies an important amount of vitamin D. The various relationships of the components of human milk, including the calcium to phosphorus ratio, are such that calcium and phosphorus are more efficiently utilized from this food than from cow's milk. It is well known that rickets is less common among breast fed than among artificially fed infants. Nevertheless, breast fed babies sometimes develop rickets and the calcium and phosphorus retentions of babies receiving human milk are increased when vitamin D is given. The requirement of the breast fed baby for vitamin D is not known accurately, but probably it is little or no different from that of the artificially fed baby, as discussed subsequently.

In the preceding discussion certain large differences in body composition between breast fed and artificially fed babies have been mentioned. The significance of these differences to the baby is not clear. Our present knowledge does not seem to warrant the selection of one type of composition as preferable to the others. Detailed nutritional studies have not proved any inferiority of human milk as compared to cow's milk in infant feeding despite the facts that certain essential components are present in small amount and that well managed artificial feeding produces a type of body composition that might seem more desirable from certain theoretical points of view. The usual reasons advanced for preference for the feeding of human milk are trite, though largely correct. These reasons pertain to ease of digestion and low bacterial content of the milk, relative freedom of the infant from infection, infrequency of digestive disturbances, production of good growth and physical status, infrequency of serious illness and relative ease of diet regulation. It may be, as so often is stated, that nature intended human milk for the human infant and cow's milk for the more robust stomach and more rapid growth of the calf. However, nature has not informed us so clearly as to when other foods should be added to the diet and what foods should be given. For answers to these questions we must

22. Drummond, G. C.; Gray, C. H., and Richardson, N. E. G.: *Antirachitic Value of Human Milk*, *Brit. M. J.* **2**: 757-760 (Oct. 14) 1939.

23. Bechtel, H. E., and Hoppert, C. A.: *Seasonal Variation of the Vitamin D in Normal Cow Milk*, *J. Nutrition* **11**: 537-549 (June) 1936.

depend on empirical practice as modified from time to time by scientific observation. That certain food components should be added early seems clear.

SUPPLEMENTS TO THE MILK DIET OF THE INFANT

Vitamin C.—Most babies at birth have blood levels of ascorbic acid of at least 0.7 mg. and some 1.0 mg. or more for each hundred cubic centimeters of blood.²⁴ The blood level decreases promptly and rapidly. By the tenth day the artificially fed baby may be expected to have approximately 0.4 mg. for each hundred cubic centimeters of blood, a prescorbutic level. By the fourth or fifth day the breast fed baby is receiving ascorbic acid in significant amounts, but in the case of the artificially fed baby the custom of delaying vitamin C administration until the second month is altogether too common. Orange juice, the most frequently used source, even though started late, is commonly given in amounts much too small to meet the need. The young artificially fed baby has been found to need approximately 20 mg. of ascorbic acid daily in addition to the small amount in the formula in order to have a blood value for this material comparable to the lower blood levels of breast fed babies. Thus at least an ounce of orange juice is desirable, beginning in the early days of life. By the time the baby is 3 months old the amount of orange juice given could well be two ounces or even more. In the private practice of pediatricians "intolerance" of orange juice is encountered frequently, but in hospital practice this condition is found most rarely; thus, certain inferences are obvious. From the point of view of digestion, orange juice is little more than a 10 per cent solution of dextrose, a material which should not disturb the alimentary tract of the most delicate infant. Perhaps it is not a coincidence that babies who cannot tolerate orange juice also usually have difficulty with tomato juice. For those who are intolerant to these food materials, ascorbic acid is widely available in tablet form.

Vitamin D.—The need for vitamin D from special sources exists from birth. One good argument favoring

24. Braestrup, P. W.: The Content of Reduced Ascorbic Acid in Blood Plasma in Infants, Especially at Birth and in the First Days of Life, *J. Nutrition* **16**: 363-373 (Oct.) 1938. Mindlin, R. L.: The Relation between Plasma Ascorbic Acid Concentration and Diet in the Newborn Infant, *J. Pediat.* **13**: 309-313 (Sept.) 1938.

the use of milk fortified with vitamin D is that probably no one hesitates to prescribe this type of milk for the earliest formulas, whereas perhaps the majority of physicians wait several weeks or into the second month before prescribing a fish liver oil. Fish liver oils in appropriate amounts may be expected to produce no digestive difficulties at 1 to 2 weeks of age. The condition most to be feared at this early age is lipoid pneumonia produced by aspiration of the oil. It is partly for this reason that some physicians use concentrated preparations of vitamin D in preference to cod liver oil. Other and perhaps preferable alternatives exist. Preparations of both vitamin D₂ and D₃ are commercially available in solutions which are freely miscible with the milk formula and offer the advantage of dispersion of the vitamin, in which state it is more efficiently utilized than in the concentrated form.

The requirement for vitamin D has been set at 400 units daily by the Food and Drug Administration; 400 to 800 units is the daily allowance recommended by the Food and Nutrition Board of the National Research Council; 2 teaspoons of minimum standard cod liver oil (approximately 600 units) is the daily dosage suggested by the Council on Pharmacy and Chemistry of the American Medical Association. No acceptable evidence has been found that a normal infant needs more than 350 units daily for optimum or for maximum calcium utilization when the vitamin D is of no greater concentration than exists in cod liver oil.²⁵ The 2 and 3 teaspoons of cod liver oil commonly prescribed contain as much as 1,800 and 2,700 units respectively when some of the high potency oils are used. Some evidence exists that these larger amounts are detrimental in that appetite decreases after several months of use, with consequent decrease in calcium retention and in growth rate.²⁶ One teaspoon daily of the less potent of the acceptable cod liver oils or ½ teaspoon of the highly potent oils is adequate. If preparations of such concentration as viosterol must be used, a dosage of 4 or 5 drops is preferable to the 10 drops commonly used. The dosage of vitamin D should be considered in terms of

25. Jeans, P. C., and Stearns, Genevieve: The Human Requirement of Vitamin D, *J. A. M. A.* 111:703-711 (Aug. 20) 1938; in *The Vitamins, A Symposium*, Chicago, American Medical Association, 1939, chapter 26, pp. 483-512.

26. Jeans, P. C., and Stearns, Genevieve: The Effect of Vitamin D on Linear Growth in Infancy: II. The Effect of Intakes above 1,800 U. S. P. Units Daily, *J. Pediat.* 13:730-746 (Nov.) 1938.

units; volumes should be stated only in interpretation to the caretaker of the infant in relation to the specific product to be used.

Cereals.—It is the almost universal custom in this country to prescribe cereal as the baby's "first solid food." The age at which cereal is given to infants has varied with different generations of physicians, but at the present time the addition of cereal to the diet at 3 months is a common practice. This current practice finds its counterpart in the time of the Roman Empire. Thus it is an empirical custom, its continuance being based on the clinical impression and belief that babies thrive better when receiving cereal. Among the cereal products listed as suitable for infant feeding are farina preparations, foods which presumably add little to the nutritional value of the infant's diet.

Earlier in this review has been mentioned the importance of supplementing the milk diet of the infant with foods containing iron and thiamine and possibly other members of the vitamin B complex. Whole grain cereals and especially fortified proprietary cereal foods contribute importantly to the satisfaction of these needs. Thus an empirical custom receives support from modern scientific evidence, but only when cereal foods are carefully selected.

It is a custom of a few physicians to defer the feeding of cereals until the second half of the first year and to supply the needed iron and B vitamins from egg yolk, vegetables and fruits. When these foods are given in appropriate quantities the supply of iron and B vitamins is somewhat greater than from whole grain cereals, though not greater than from some of the fortified proprietary foods. Thus among the natural foods the known needs of the infant are supplied better from egg yolk, vegetables and fruits than from whole grain cereals. When these foods are given, the feeding of cereal loses much of its importance and may be deferred until the capacity of the infant increases to the extent that the entire group of foods may be taken comfortably.

OTHER SUPPLEMENTARY FOODS

Some of the food values of egg yolk, vegetables and fruits have been mentioned in the preceding section. Egg yolk is frequently given, preferably cooked, at 3 to 4 months of age, sieved vegetables at 4 to 5 months

and sieved fruits at 4 to 6 months. The giving of a variety of these foods twice a day instead of the usual cereal twice daily not only supplies needed nutrients but helps to accustom the infant to variety in flavors and textures of foods, a goal highly desirable from the point of view of forming good feeding habits.

THE PSYCHOLOGY OF INFANT FEEDING

The psychologic aspects of infant feeding are fully as important as those more obviously nutritional. One of the commonest complaints relating to children brought to the pediatrician is anorexia, usually dependent on training in feeding habits and usually having its origin in infancy. Often the formula prescription of the physician contributes to the onset of the difficulty. A definite volume of food is prescribed, and the conscientious and solicitous parent endeavors to give this exact quantity of formula at each feeding regardless of possible variations in appetite. In this manner rebellion against food may have its beginning. The desirability of variety in texture and flavor has been mentioned. These variations should be introduced early. The child who has had only liquid and sieved foods throughout the first year frequently refuses coarser foods when they are finally offered. At least some of the fruits and vegetables offered should be chopped or mashed rather than sieved after the sixth or seventh month. The continuance of bottle feeding after 1 year of age is not good feeding practice and is usually evidence that other environmental factors probably are faulty.

THE FEEDING OF CHILDREN

The conclusion is reached easily that the diets of our children have improved in many ways over those used in the past. It is clear also that they have not yet improved sufficiently even in those economic levels at which the cost of food is relatively unimportant.

It is customary to attribute increased rate of growth of a population group to improvement in nutrition. Certainly it has been demonstrated that nutrition definitely affects the rate of growth. Whether the cause is nutritional or dependent on some other factor at present unrecognized, studies have shown that young people of this country are taller and heavier than were

the children of former years. For example, Meredith²⁷ has shown that boys living in the United States today are 6 to 8 per cent taller and 12 to 15 per cent heavier than was the case half a century ago. He found the size of boys to be related to economic status, presumably a nutritional relationship. He found also that differences in size were unimportant when related to geographic distribution within the United States.

Other studies have shown that well fed babies and children grow at rates greater than average. The growth data of Kornfeld²⁸ (1929) and of Stuart²⁹ (1934) show a growth rate more rapid than the data of Baldwin³⁰ (1921). Though these differences are greater among infants, they appear also for the child. The assumption seems justified that the increased growth rates are attributable to improved nutrition.

Several approaches exist to the obtaining of evidence that current diets are not satisfactory. One of these is to point out the frequency of dental caries and the dependence of tooth decay on faulty diet. This field of observation is highly controversial in some respects, but numerous investigators have presented evidence of interrelationship between caries and dietary content. A critical review of the evidence would be too involved and lengthy to permit inclusion here. Various investigators have emphasized the importance in the diet of sugar, calcium, vitamin D, ascorbic acid, fluorine, refined foods and the adequacy of the diet as a whole.³¹ Nearly all investigators in the field will agree to the importance of one or more items of this list in relation to dental caries. All the items relate to nutrition or at least to diet content. Another approach to the determination of the adequacy of the diets of the population is by means of surveys. Such surveys indicate widespread dietary faults which undoubtedly affect nutrition according to the degree of fault. Estimates

27. Meredith, H. V.: Stature and Weight of Children of the United States, *Am. J. Dis. Child.* **62**:909-932 (Nov.) 1941.

28. Kornfeld, Werner: Zur Bewertung von Grösse und Gewicht bei Knaben und Mädchen aller Altersstufen, *Ztschr. f. Kinderh.* **48**:188, 1929.

29. Stuart, H. C.: Standards of Physical Development for Reference in Clinical Appraisal: Suggestions for Their Presentation and Use, *J. Pediat.* **5**:194-207 (Aug.) 1934.

30. Baldwin, B. T.: The Physical Growth of Children from Birth to Maturity, University of Iowa Studies, University of Iowa, Iowa City, 1921, vol. 1, no. 1.

31. Advisory Committee on Research in Dental Caries: Findings and Conclusions on Its Causes and Control, Compiled for the Research Commission of the American Dental Association, Lancaster, Lancaster Press, 1939.

of the prevalence of nutritional deficiency have been published recently.³²

One nutritional essential commonly deficient in the child's diet is vitamin D. Many children receive an inadequate amount from sunshine in summer and few receive a sufficient amount in winter. While giving vitamin D preparations has become routine in infancy, relatively few mothers realize that this material is important throughout the growth period. Without vitamin D, children vary widely in their ability to utilize calcium and phosphorus; for some the utilization is excellent, for others poor. Since the distinction between these two types of children cannot be made without prolonged and detailed special study for each child, it is appropriate to consider that all children require vitamin D. When the calcium and phosphorus intakes are adequate and appropriate, from 300 to 400 units of vitamin D daily will produce retentions of these minerals ample to satisfy the theoretical requirements for normal growth.²⁵

Except for special therapeutic purposes, probably no need exists for special preparations of vitamin A to be given in addition to that present in the diet. Evidence is conflicting concerning the frequency of vitamin A deficiency among the children of this country. Certainly vitamin A is relatively abundant in many of our foods, and any reasonably good diet contains ample not only to meet the minimum requirement but for storage. It is clear also that if the diet is fortuitously deficient in vitamin A it is deficient also in many other essentials and that much more is needed than addition of vitamin A alone. It is believed that in a high proportion of instances in which children are found to have clinical evidence of vitamin A deficiency the deficiency is dependent on defects of utilization in greater measure than on dietary deficiency.³³ Infections and illnesses produce prompt response in impairment of utilization. In the continued presence of illness large therapeutic doses of vitamin A may be required to supply the need or these large doses may fail to produce a noticeable effect.

32. Jolliffe, Norman; McLester, J. S., and Sherman, H. C.: The Prevalence of Malnutrition, *J. A. M. A.* **118**: 944-950 (March 21) 1942. Jolliffe, Norman: Nutritional Failures: Their Causes and Prevention, *Milbank Memorial Fund Quarterly* **20**: 103-125 (April) 1942.

33. Jeans, P. C.; Blanchard, Evelyn L., and Satterthwaite, F. E.: Dark Adaptation and Vitamin A, *J. Pediat.* **18**: 170-194 (Feb.) 1941

Dark adaptation tests have a definite field of usefulness in determining vitamin A status, though this issue has been clouded greatly by misinterpretation. In dysadaptation from utilization deficiency dependent on illness, subsequent improvement has been attributed to increased proficiency produced by practice in the test because no extra vitamin A had been given. Failures to correlate the test results with dietary intake of vitamin A have been used to condemn the tests when all subjects had adequate intakes and gave test results within the normal range. Uncritical reading of such reports has led to confusion in acceptance of the validity of the tests. That dark adaptation tests have found acceptance in authoritative groups is attested by the fact that the vitamin A standards set up by the Food and Drug Administration and by the Food and Nutrition Board of the National Research Council were based chiefly on the results of adaptation tests.

Much circumstantial evidence exists in recent literature to the effect that thiamine probably is obtained by many children in amounts less than those considered appropriate or optimum.³⁴ It is clear that the remedy for this situation, to the extent that it exists, lies in a better selection of dietary components rather than in the giving of special preparations of thiamine. In general, refined cereal preparations are to be avoided except as they have been "enriched." The lower the economic level, the greater the extent to which the energy need usually is supplied by refined cereal products and sugar, sometimes amounting to 50 per cent or more of the total energy intake. Enriched bread and flour have now become available at all economic levels. Much ado has been made over the increasing consumption of refined sugar, some believing that sugar is harmful per se, but all agreeing that it is too likely to replace foods nutritionally valuable. It is refreshing to find another point of view as presented by

34. Wilson, H. E. C.: Pyruvic Acid Test for Thiamine Deficiency in Children, *Lancet* 1: 199 (Feb. 14) 1942. Mason, H. L., and Williams, R. D.: The Urinary Excretion of Thiamine as an Index of the Nutritional Level: Assessment of the Value of a Test Dose, *J. Clin. Investigation* 21: 247-255 (March) 1942. Wortis, Herman; Goodhart, R. S., and Bueding, Ernest: Cocarboxylase, Pyruvic Acid and Bisulfite Binding Substances in Children, *Am. J. Dis. Child.* 61: 226-230 (Feb.) 1941. Schlutz, F. W., and Knott, Elizabeth M.: Cocarboxylase Content of Blood of Infants and of Children, *ibid.* 61: 231-236 (Feb.) 1941. Melnick, Daniel: Vitamin B₁ (Thiamine) Requirement of Man, *J. Nutrition* 24: 139-151 (Aug.) 1942. Lane, R. L.; Johnson, Elizabeth, and Williams, R. R.: Studies of the Average American Diet I; Thiamine Content, *ibid.* 23: 613-624 (June) 1942.

Macy.³⁵ It has been her observation that, the better the diet from the nutritional point of view, the less the desire of the child for sugar. She has concluded that the amount of sugar taken voluntarily by a child is an excellent criterion of the adequacy of the diet. As the diet is improved, the voluntary ingestion of sugar decreases. If this observation is correct, the point of attack is not to restrict sugar but to improve the diet by increasing the amounts of nutritionally valuable foods offered.

Thiamine is reputed for its effect on the appetite. An important proportion of the children for whom parents seek medical advice are brought to the physician because of anorexia. In few of these instances is the anorexia correctible by thiamine medication. Though the child may be receiving suboptimal amounts of thiamine and other essentials, the fundamental difficulty lies in the environment and training in feeding habits, these bad habits often having had their origin early in infancy. The correction of these habits has little relationship to thiamine.

Vitamins other than those mentioned need little special discussion. A child who ingests his expected allowance of milk receives from this source alone most, if not all, of the riboflavin required. For the child who does not receive his quota of milk, the possibility of deficiency not only of riboflavin, but of other essentials as well, is to be considered, and the diet must be supplemented accordingly in a special and expert manner if it is to be complete. Meat, particularly the glandular organs and lean pork, is a good source of the B group of vitamins. If ingested regularly, it is a better source of thiamine and niacin than is milk; though it is a fairly good source of riboflavin, it is inferior to milk in this respect. Eggs contribute importantly to the supply of B vitamins as well as other nutritional essentials and should be included in the diet frequently, preferably daily.

Calcium is the mineral requiring chief attention in childhood, since the other essential minerals are more likely to be present in sufficient amount in most diets. Milk and milk products are our best food source of calcium. In the case of the young child the usual diet, exclusive of milk, contains approximately 0.2 Gm. of

35. Macy, Icie G.: *Nutrition and Chemical Growth in Childhood*, vol. I, Evaluation, Springfield, Ill., Charles C Thomas, 1942, pp. 84-85.

calcium; the diet of the older child contains approximately 0.3 Gm. The remainder of the requirement of 1 to 1.5 Gm. is normally supplied by milk. Thus with propriety one may speak of the milk requirement in relationship to the calcium need.

A curve of theoretical requirement for retention of calcium may be constructed by apportioning according to rates of growth at different ages the total accretion of calcium from birth to maturity. When such a curve is constructed, the daily retention requirement is found to decrease from approximately 300 mg. in infancy to a low point of about 180 mg. early in the preschool period, then to increase to about 450 mg. at the beginning of adolescence.³⁶ The efficiency of children in calcium utilization varies widely, but, when vitamin D is given, the range of retention is not great, though always the amount ingested exceeds greatly the amount retained. Discussing the calcium requirement in terms of milk, it has been found that during the early part of the preschool period 1 pint of milk in addition to the usual diet permits retentions adequate to meet the theoretical retention requirement, which is low at this age.³⁷ Very quickly after this time and up to approximately 10 years of age the retention requirement is not met until the quantity of milk is increased to 1½ pints daily. The requirement during adolescence is not known with the same degree of definiteness but probably is the calcium content of 1 quart of milk daily. It seems unwise to place any emphasis on the low requirement in the early preschool period. This period is brief. More is received by the baby immediately preceding this period and more is required subsequently. Milk should not be considered solely as a source of calcium. It contributes most importantly to the protein requirement as well as other essentials. Consequently it seems preferable to advise at least 1½ pints of milk after the period of infancy and up to the age of 10 years. The taking of a full quart of milk throughout this period can be considered as bene-

36. Jeans, P. C., and Stearns, Genevieve: Unpublished data.

37. Daniels, Amy L.; Hutton, Mary K.; Knott, Elizabeth M.; Everson, Gladys, and Wright, Olive E.: Relation of Ingestion of Milk to Calcium Metabolism in Children, *Am. J. Dis. Child.* **47**: 499-513 (March) 1934. Daniels, Amy L.; Hutton, Mary K.; Knott, Elizabeth M.; Wright, Olive E., and Forman, Mary: Calcium and Phosphorus Needs of Preschool Children, *J. Nutrition* **10**: 373-388 (Oct.) 1935. Outhouse, Julia; Kinsman, Gladys; Sheldon, Dorothy; Twomey, Irene; Smith, Janice, and Mitchell, H. H.: The Calcium Requirements of Five Preschool Girls, *ibid.* **17**: 199-209 (March) 1939.

ficial only, provided the larger quantity does not crowd from the diet other essential foods. The fear or belief that the larger quantity may have this effect is widely prevalent but not too well founded, especially for those children who have normal appetites.

Calcium deficiency, at least in moderate degree, is believed to be widely prevalent in childhood. To whatever degree such a situation exists, it is usually much worse during adolescence. At this age period the requirement is increased and too often the intake not only is not increased but actually is decreased, sometimes because of a desire, especially in girls, to remain slim. It is during the adolescent period particularly that dental caries tends to become rampant, a condition believed by many observers to depend on nutrition and by some observers to depend in part on calcium metabolism.

The custom of prescribing or using calcium salts is widely prevalent. Such salts have a definite field of usefulness under special circumstances, but they have no rightful place in the normal diet. When they are used, they should be carefully chosen for the purpose intended and the dosage should be more nearly adequate than it frequently is. The phosphates of calcium are as well utilized as the same salts in milk. The calcium needs for growth can be satisfied easily by means of these preparations. In order that calcium may be usable for growth, it is necessary that a proportionate amount of phosphorus be available at the same time. The calcium of such salts as calcium lactate and gluconate is utilizable for retention only to the extent that phosphorus is present otherwise in the diet. All diets contain at least a fair amount of phosphorus, but the amount usually is not adequate to permit the best use of the calcium of these salts. The chief objection to the customary use of calcium salts is that they are not food in the usual sense and they are often used as a substitute for milk. It is obvious that calcium salts can be a substitute for milk in only a most restricted sense and that the diet must be supplemented in many additional ways in order to compensate for the absence of milk.

The possibility of protein deficiency in the diets of children has received some, but insufficient, attention. One of the criteria which may be used for estimating

the protein content of the body is the creatinine output in the urine. Creatinine excretion is directly proportional to the amount of muscle in the body.³⁸ When children are fed ample protein, the creatinine excretion (consequently the amount of muscle) rises to a constant level for each child, with a narrow range at each age period for a group of children.³⁹ When these values are plotted according to age and in terms of creatinine for each kilogram of body weight, a curve is obtained which may be considered as representing normal conditions as regards creatinine output and muscle mass. Creatinine data collected from the literature, as well as data from this clinic, show that the great majority of children studied have creatinine values below, often considerably below, the theoretically normal curve when they first come under observation. Those with normal values are the exception rather than the rule. In all the instances in which observations have been made the creatinine output increases promptly to the normal level when amounts of protein are fed which are consistent with what are considered standard dietary allowances. It appears that when children receive suboptimum amounts of protein they approach as nearly to the normal creatinine excretion as their protein intakes permit them. It is of interest also that the weight of the child may be, and in fact usually is, within what is considered the normal range when the low creatinine values are observed. The size or weight of the body is not a criterion for judging protein metabolism.

In meeting the protein requirement, emphasis is to be placed on the value of milk. A quart of milk daily supplies most of the protein need of the young child and half the need at the beginning of adolescence. Such a quantity of milk contributes more protein to the diet than any other single food. When milk is excluded from the diet, the protein requirement of the child can be met only if special and expert supervision is given.

SUMMARY

Despite all our modern knowledge of infant nutrition and all the current refinements of artificial feeding, feeding at the breast of the mother remains an ideal

38. Hunter, Andrew: *Creatine and Creatinine*, London, New York, Longmans Green & Co., Ltd., 1928.

39. Stearns, Genevieve, and others: Unpublished data.

procedure. This is true despite the fact that human milk contains only a bare minimum of most of the nutritional essentials and the fact that the body composition of the breast fed infant departs widely from that which preceded and that which follows, in contrast to the body composition of the artificially fed baby, which maintains more closely a smooth continuance of the fetal and postinfancy curve.

Vitamin D is needed early by all babies, whether breast or artificially fed. Vitamin C is needed early by artificially fed babies and is a harmless safeguard for the breast fed baby. No need for vitamin A from special sources exists. If current custom is in error, it errs in the direction of giving too much vitamin D and too little vitamin C and in not giving either of these materials early enough.

Additional supplementary foods should be given at not later than 4 months of age to both breast and artificially fed babies. One important function of these supplements is to supply iron and vitamins of the B group. Another function is to accustom the baby early to variety in flavor and texture for the promotion of good feeding habits. Anorexia and poor feeding habits, which occur so frequently in older children, often have their origin in feeding mismanagement in infancy.

In a general way we have done reasonably well nutritionally by our babies, but not so well for children past infancy. The nutrition of the child has been improved during the past generation, but not to the extent desirable or possible with present knowledge. Though observers do not agree too well as to the particular nutritional or dietary factors responsible for dental caries, nearly all are of the opinion that one or more dietary components may be responsible, either by lack of those which are essential or by the presence of some considered harmful. On such a basis, dental caries is our most widespread nutritional scourge.

At least three nutritional essentials deserve special emphasis in childhood, viz. vitamin D, protein and calcium. Vitamin D is required throughout the growth period, a fact extensively overlooked. Milk as our only constant good food source of calcium is not taken in sufficient quantity by a large number of children. Protein deficiency is much more common than is

generally realized. A diet adequate in protein cannot be arranged fortuitously without the inclusion of milk.

Though thiamine is obtained by a large proportion of children in quantities scarcely meeting their needs, the remedy lies in better food selection, not in thiamine medication. Enrichment of flour and bread and decreased consumption of sugar should contribute materially to the desired end.

Vitamin A from special sources is not needed by the normal child. A diet fortuitously deficient in vitamin A is deficient also in other respects. The remedy is a better diet, not medication.

CHAPTER XIX

FEEDING THE AGED

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At the outset I present five reasons why practicing physicians should become interested in the problem of feeding the aged. When they convince themselves that overindulgence and needless restriction in food are both wrong, then will their patients gradually conform. They always have conformed and on many occasions have accepted guidance far less scientifically sound than that outlined in this series on nutrition.

1. Those living over 60 are now so numerous that their individual needs call for an active aggressive medical approach. The individual, instead of his disease, is our problem. We must become guides or umpires rather than healers and on a long term, rather than a temporary, basis.¹ The treatment of diabetes with balanced diets and insulin, of pernicious anemia with liver extracts, illustrates the technic. We have asked repeatedly that we be allowed to keep the "physician-patient" relationship. Here is our opportunity.

2. Mass efforts (for preventable diseases) and specifics (for certain infections) have nearly eliminated many common diseases (diphtheria, typhoid). We are on the way to control pneumonia if seen early. Less young people die; more attain advanced age unhampered by a holdover of morbidity from earlier nonfatal encounters that nevertheless leave their scars.

3. The competence of healthy older people is largely a matter of nutrition. Doctors also have an age problem. They also age. America is at war. There is no turning back. Physicians attain their fourth decade before they become active in their respective fields. They need more years of activity after 60 than most are

1. Causes of Death, Statistical Department, Metropolitan Life Insurance Company, 1940: Of children born:

	1900	1940
Acute deaths	1 of 3	1 of 6
Chronic disorders	2 of 4	3 of 4

"The only chronic malady showing striking decrease is tuberculosis."

avored with. Coronary disease is all too common with doctors. I shall refer to it at some length because food excesses (fat) may be a factor involved.

4. Population is an asset. Human beings must never be classed as liabilities. Guiding the aging may be made a stimulating medical field. It is not a "second childhood" affair, as the uninformed facetiously imply. Geriatrics is less a science than an art. It is not an isolated specialty comparable to pediatrics. The pediatrician tells the mother or nurse what to feed the child. If the food is available, the child usually gets it. The geriatrician (I do not aspire to be one) usually finds his older subjects neither acquiescent nor especially cooperative. Food habits have become fixed; those under or over eating enjoy their self determination. Accordingly it is not sufficient to tell off average menus suitable for the old. This simple assignment I leave to the scores of available diet manuals. Some argument must be presented to give the whys and wherefores of the need of balance in various foodstuffs and vitamins. The overrefinement of starch and excessive use of sugar must be warned against and the reasons made clear enough so that appetite is not the sole guide to eating. All specialists and general practitioners giving service to the old should familiarize themselves with the researches in nutrition now contributing so effectively where understood and applied.

I shall attempt to assemble the evidence establishing adequate nutrition as the present day primary need of the older age group. The previous chapters in this series have authoritatively outlined the increment in knowledge of nutrition that has come since the turn of the century. McLester in the introductory chapter expressed the fear that, despite all these advances, there may follow an undue lag before this nutritive beneficence becomes a part of our life and heritage. It rests with practicing physicians to limit this lag, to bring about within as few decades as possible (especially for the older age group) something comparable to the improvement in nutrition that has already come to two generations of babies since pediatricians have put the balanced nutrition into effect.

5. We have the present war emergency. There is much salvage within the old age group. No portion

of the present nutritional program should be denied the aged on any basis dictated by their years. Age is hard to define. It is known best by what it does. It limits outlook and capacity; it adds its "aches and qualms," all too readily attributed to ingested food. The food left out may contain the elements that complete the vicious circle, so that less food, more infirmity, more symptoms, less efficiency pile up. Age conceals a vast reservoir of talent, skills, wisdom and experience, not to mention much muscle and brawn if proper food maintains reserve. There could not be a better time to plan a purposeful nutritional program for the peace that must follow war. Doctors must take part in it.

TABLE 1.—*Age Level Extensions* *

	1900	1927	1940
Average age at death	26.79†	58.65	62.00
Death under 1 year	24%	5%	5.2%
Death over 75	4%	25%	32.1%
Death at 45 or over	24%	79%	83%

* Statistics furnished through Dr. Mario Fischer, Duluth Health Commissioner.

† There was at that time a high death rate from typhoid and tuberculosis, as well as from complications of all the contagious diseases of childhood. In the summer time there was the traditional high death rate from feeding disturbances in children, and pneumonia was prevalent in the winter. Many woodsmen and miners came into Duluth for terminal hospitalization.

This is a machine war—the product of a machine age. In our depression years unemployment, broken homes, improvident children, impractical subsistence relief or pensions, robbed the old of employment, position, honor and a place in the community. With such crying need for all possible man and woman power it is now or never for us to give back to this group some of what they have lost.

LIFE EXTENSION; FOOD AVAILABILITY; EMPLOYMENT

Life extension has brought great social and economic problems (table 1). I shall add but few of the figures now so freely quoted. The most striking prediction concerns that "22,000,000 people in the United States over 65 years of age" within another generation. Up to the time of our engagement in the war efforts and for ten previous depression years, youth was held back

from production. Those discharged over 50 found industry hesitant to reemploy them. Now we face a condition where retirement after 65 promises less and less as taxes and living costs mount, as investment possibilities narrow and pensioners multiply. In the offing there is always the specter of inflation. At present few people think of leisure or retirement; it is timely to emphasize the great advantage of cultivating health, mental poise and technical skills and avoiding obsolescence. Since the turn of this century the life expectancy of white babies has been advanced sixteen years for females and fourteen for males. This totals up to 67.31 for the former and 62.94 for the latter. The immediate and pressing issue is How may these years be made worth while? Food is a basic requirement; the amount and proportion depend on the individual and where and how he lives. It may be said, with few exceptions, that to deny people work is to deny them food. Now, when production is so much in the forefront of our national demands, we must salvage everything possible, and certainly not the least item in this effort is the group concerning which I write. If justice is ever to obtain, the appeal "Give us this day our daily bread" must exclude none. The way to give it is to plan that all able shall work; doles and subsistence are mockeries. This is a peace program with which a war schedule must be implemented. Otherwise we shall still be at war, for with the military peace we shall continue economic war.

THE FALLACY OF FOOD RESTRICTION FOR THE AGED

A stupendous literature dealing with nutrition accumulates. I append references to certain authors where some may wish to know the source material. The resurgence of interest in dietetics has come at the same time with a reviving interest in medical geriatrics. Many² have written articles based on the medical needs

2. Tuohy, E. L.: A Proper and Adequate Protein Diet for Elderly People, *Minnesota Med.* **25**: 313 (May) 1940. Norman, J. F.: Our Aging Population, *ibid.* **24**: 1066-1071 (Dec.) 1941. Christian, H. A.: Some Limitations in Preventive Medicine, *Ann. Int. Med.* **12**: 1499-1506 (March) 1939. Dublin, Louis I.: Medical Problems of Old Age, University of Pennsylvania, Bicentennial Conference Bulletin, Metropolitan Life Insurance Company of New York. Wilder, R. M.: Nutrition in United States: Program for Present Emergency and Future, *Ann. Int. Med.* **14**: 2189-2198 (June) 1941. McCay, C. M.: Diet and Aging, *J. Am. Dietet. A.* **17**: 540-545 (July) 1941.

of the aged. There is a new edition by Thewlis³ bringing up to date the pioneering of Nascher; a recent handbook by Boas⁴ dealing with the treatment of the patient after 50 is well arranged and documented, and considerable attention is paid to diets. Cowdry's⁵ compendium from various authors, including physiologists, biochemists and psychologists, is most readable and informative. Some readers will be displeased that so few positive factual statements may be made. People around the world live well on the most varied diets, each satisfactory as decreed by custom and availability. If the reader would like an American menu for elderly people, there are available countless articles where these may be consulted and individual tastes consulted. Some statements might be "factual" if more were known about aging as a process.

For reasons hard to understand, there is the widest belief that the elderly should be abstemious. The few gluttonous and obese have visited this inhibition on the many who are overconscientious and underweight. We should start with the dictum of Piersol and Bortz⁶ "To add life to years rather than years to life." That is the basic motive for campaigning for better nutrition for the aging. What we are looking for is not a dragging out of vegetative almshouse existence but the promotion of real efficiency. The human being attains his full bodily development, let us say, by 40, the beginning of his fifth decade. His next decade and a half pits him against the most stressful period of his life: the time in which early rheumatic and other infections mature and cripple; when arterial hazards (coronary disease) add their tragic interruptions; when metabolic perversions (obesity, diabetes and gout) appear—all when his business, his insurance plans, his educational and family responsibilities are at their height. And this is the period when we ask him to prepare himself for the seventh, eighth and ninth decades which present life extension tables plainly tell him are "just around

3. Thewlis, M. W.: *Geriatrics a Special Branch of Medicine*, M. Rec. **153**: 433-435 (June 18) 1941; *The Care of the Aged (Geriatrics)*, St. Louis, C. V. Mosby Company, 1941.

4. Boas, Ernest P.: *Treatment of the Patient After Fifty*, Chicago, Year Book Publishers, 1941.

5. Cowdry, E. V.: *Problems of Aging*, Baltimore, Williams and Wilkins Company, 1939 (Josiah Macy Jr. Foundation Publications).

6. Piersol, G. M., and Bortz, E. L.: *The Aging Process: Medical-Social Problem*, Ann. Int. Med. **12**: 964-977 (Jan.) 1939.

the corner." This is no longer a promise or objective, it is with us here and now and in very formidable proportions. Dominant as heredity is known to be, we may just as well leave it out of the discussion. Each individual must accept the genetic complement fate has assigned him. He must make the most out of what he has. It must be clear that no one may expect the most from the later age decades when no preparation has been made in adjusting habits, cultivating something of a philosophical attitude toward life and its responsibilities and at least looking about among friends and neighbors for object lessons or examples of men and women who are succeeding in various stations and walks of life in arriving at what we call a comfortable and serene old age. Age is feared much more for the restrictions it may impose than the promise of death. The body as well as the mind must be trained to accept aging. The time to acquire the physical and mental deportment with which to get the most out of life in its later decades is in middle age. The neurosurgeon cannot acquire his skill for the successful removal of a brain tumor when the patient with a terrific headache enters his consulting room. The cultivation of proper food habits early in life is too obviously advantageous to call for further discussion or elaboration. We must learn to grow old skilfully as well as gracefully.

Perhaps "the less food for old people" fallacy hinges on the supposition that for them energy for current expenditure is the chief item and therefore carbohydrate and some fat with a minimum of protein suffice. In any case, that is the way many old people exist but do not live. All living creatures are interrelated and follow universal laws in their metabolism and growth. Life and its products are handed back and forth between living creatures (plant and animal). Nature has provided these laws of balance and coordination. Simpler organisms accept them, but man has varied notions of his own. He chooses primitively with the least cultivated of his tastes. The result is a diet over-rich in refined flours and sugar. He misses the balanced assemblages plant life has integrated and domestic animals have concentrated for him. They do it better than he can plan it. Hence the appeal for natural foods, including animal products. Human growth is not terminated when adult stature is attained. Witness the manner in which the

atrophic smooth tongue of addisonian anemia assumes normal size and coating after optimal exhibition of liver. The Lawrences have shown with Geiger counters how rapidly tagged iodine is picked up by the thyroid. Tagged calcium has been located promptly in tooth enamel, long supposed to be fixed, inert and final for the duration of life. Rates of growth vary, but the process endures with life. Repair within the body is a continuous process and in such organs as the liver may be stupendous. Fixed and overspecialized cells (retina) must also be undergoing some change, as is disastrously connoted when the blood supply is even temporarily interrupted. In that sense reproduction of the individual as a unit is limited by age, but, in the cellular domain, active living processes demand nitrogenous equilibrium continuously. The tea and toast schedule for grandma is outmoded. No old person is a walking museum piece—a holdover from last year's crop—and for the same good reason must not be treated like a barnacle on the ship of state.

Stieglitz⁷ has used the term gerontology to cover a study of the aging process, in contrast to geriatrics (care of the elderly). The distinction is proper. Simms⁸ has studied Dublin's insurance mortality records and computes that our young adolescent at age 10 is the healthiest human being: only one in eight hundred dies at that age. He states that if such a mortality were maintained the life span would stretch out to 550 years! Age, as a name for what Shakespeare meant, when he wrote "We ripe and ripe and ripe; and then we rot and rot and rot," while indeed baffling to scientists, is very obvious to women of fashion. They are most familiar with what age does to the skin. Roger Bacon thought age concerned the withdrawal of water from the body and was in the nature of wilting. He was well informed; fluid balance connotes integrity. To the three great reserve organs of the body—the liver, the muscles and the skin (commonly listed)—I would presume to add the osseous system, not only for its calcium reserves, but for the housing of the

7. Stieglitz, Edward J.: The Urgency of Gerontology, News Edition, Am. Chem. Soc. 19:1147 (Oct. 25) 1941; The Potentialities of Preventive Geriatrics, New England J. Med. 225:247-254, 1941; Aging as an Industrial Problem, J. A. M. A. 116:1183-1187 (March 29) 1941.

8. Simms, Henry S.: The Problems of Aging and of Vascular Disease, Science 95:183-186 (Feb. 20) 1942.

important areas of hematopoiesis. Cannon ventures a practical explanation of age without entering into the chemist's discussion on collagen metamorphoses; he says age witnesses a gradual limitation of homeostasis wherein such body constants as acid-base equilibrium, body temperature, mineral and water balance are still maintained but within progressively narrowed limits. Physiologists strive to produce in animals counterparts of the human diseases they are studying. I was surprised in my reading to learn that not a little research has been done with the lower animals on the problem of age. Simms⁸ has made a plea for much greater financial support for research along the lines of determining how age limits physiologic responses. This is directly in line with Stieglitz's⁷ gerontology. Simms has developed a method of sublethal bleeding of standardized rats of various ages. The older rats stood the shock (Cannon-Blalock) of this bleeding with "a probability of death sixteen times greater than with the younger rats." Dearing,⁹ experimenting with digitalis and its toxic effect on the heart, brain and coronary blood flow, found that his older animals did not withstand the drug nearly as well as the younger. One turns from these laboratory experiments to the obvious deductions of the sports writers. The prize fighter is out by age 30, the baseball player by 35, and now we are told that, to meet the demands of the "blackout" incidental to dive bombing, only the youngest aviators are able to withstand this rigorous test. Fulton¹⁰ has written on the "acceleration factor," the mechanical process by which the swerving plane drives the blood centrifugally so that the flow does not accommodate rapidly enough to the change of direction of flight so that blood attains the higher centers. So the youngest and sturdiest are chosen to sustain these enormous stresses because they better retain consciousness.¹¹ Youth is able to establish records in the shorter sprints and hurdles, but when prolonged effort is displayed

9. Dearing, W. H.: The Effect of Digitalis on the Heart, Brain, Electrocardiogram and the Coronary Blood Flow in Experimental Animals, read before the Minnesota Society for the Study of the Heart and Circulation, Rochester, Minn., Nov. 29, 1941.

10. Fulton, J. F.: Physiology and High Altitude Flying, with Particular Reference to Air Embolism and the Effect of Acceleration, *Science* **95**: 207-212 (Feb. 27) 1942.

11. According to Fulton's article, the luftwaffe has found that its youngest recruits better withstand the blackout if they have been fed large portions of beefsteak.

(distance runners, sand hog workers) older men have an advantage accruing from skill and husbanding their strength. Industrialists should remember this. Freeman¹² and others, studying shock, stress the factors of exposure, cold, fatigue, blood loss and water loss. Shock is, in part, an exaggeration of situations beginning as discomforts and mounting to dire upsets of homeostasis and challenging the integrity of the individual by dissociating the orderly functioning of system organs. Elderly people have simpler names for chills, fatigue and exhaustion. Food and drink exhilarate as does nothing else. Add sleep and you have recuperation. Periodic starvation has no place in the care and conditioning of the old and is one of many useless middle age fads. This is the background for practical suggestions I shall make in terms of when and what to eat.

FOOD AND THE CARDIOVASCULAR SYSTEM

"A man is as old as his arteries." This statement has been too long accepted by clinicians. We look at an older person and then palpate the peripheral arteries. "Peripheral vascular disease" is a category that covers many difficulties experienced by the aged. Certain chapters in Cowdry's book discuss a dissociation of aging and arteriosclerosis—the former a natural process beginning before birth, the latter an unnatural acquisition so common that many think it universal. We face a medical problem when many in the prime of life die with 1 centimeter or less of thrombus in the branch of an atheromatous coronary artery, while many octogenarians are hale and hearty with most of their larger arteries laid down in concrete. Wherein does the question of diet enter into this discussion? Is aging hastened by overeating? Does abstemiousness promise a long life? The answers to these and many similar questions are not forthcoming, but the statement by Simms that many useful years may yet be added through life extension when science discovers how to prove the aforementioned dissociations and produce specific inhibitors points the way. In the meantime we may learn something by looking about us; and, while clinical observations may be loose and indefinite, Spies has significantly

12. Freeman, N. E.; Freedman, H., and Miller, C. C.: Production of Shock by Prolonged Continuous Injection of Adrenalin in Unanesthetized Dogs, *Am. J. Physiol.* **131**: 545-553 (Jan.) 1941.

commented that our knowledge of the avitaminoses has been substantially advanced by such observations and by testing out the newer pharmacologic vitamins and ordering better foods.

There is also considerable difference of opinion as to just how much over or under nutrition exists in our country, in different states and among different classes of people. Chapter XXII (Stiebeling) will discuss that issue based on her extensive observations and studies in association with the United States Department of Agriculture.¹³ I think undernutrition produces more physiologic disturbances, but overnutrition (fat) may hasten the development of more pathologic change.

Living in a rich agricultural state, I do not see very many people needlessly undernourished. By proper planning and marketing and with attention to the methods discussed in chapter XVI (Cowgill) most of the borderline or marginal degrees of undernutrition which we uncover are economically unnecessary and stem from social maladjustment, anxiety states and outmoded medical advice. Undernutrition reduces vitality and well-being much more than it hastens decline or senility. It is hard to believe that "optimum nutrition" could endanger anybody's vascular system. The trouble lies in finding an "optimum diet"—because it varies with every locale, every people, employment and individual purpose; and nature has distributed around the world the widest assortment of adequate food sources. Some may like a "short life and a merry one"—at least at middle age that is their choice. Whatever the process by which it is brought about, 70 per cent of our Duluth Clinic¹⁴ patients are dying of cancer and cardiovascular-renal disease (including cerebral hemorrhage). This figure for cancer (18 per cent) is higher than the Minnesota State Board of Health figures (14 per cent) for 1941 and represents a higher than average of older people in our clientele. The approximate 50 per cent of cardiovascular renal disease¹⁵ is the same as Simms's claim for all deaths over age 10. I have checked these

13. This department publishes a long list of studies full of interest and information.

14. This study is part of a sampling of our records, with especial reference to the deaths. For the year 1940 and 1941, 1,339 deaths have been carefully traced, covering patients of all ages whom we have seen since 1915.

15. This is the group in which gerontologic research may be most productive (Simms).

figures from four old line life insurance companies, and I present in table 2 the results from one of them. The others are almost identical. This detail of end results tells little, of course, relative to incapacity and sickness among the group I am discussing. From many studies dealing with the prognosis in degenerative heart disease it would be fair to state that there is an average illness (partial or complete) of about two years. During that time diet is a part of the treatment and is subordinated thereto. Unless some newer food components (biotin) can be proved to be carcinogenic, preventive measures (diet) in terms of about three fourths of our deaths are very much in that current state of "too little and too late." Table 3 shows clearly enough that

TABLE 2.—*Causes of Death* *

	Year		
	1941	1931	1921
Circulatory diseases (heart disease, apoplexy and so on).....	48.2%	32.8%	25.4%
Cancer and other malignant tumors.....	10.1	10.2	10.6
Violent deaths (automobile, suicide, aviation)	9.4	10.9	14.1
Respiratory diseases (tuberculosis, pneumonia, influenza)	8.6	14.6	19.3
Digestive and genitourinary diseases (diabetes, nephritis, ulcer, liver).....	7.6	12.2	15.9

* From Provident Mutual Life Insurance Company.

the life line of our people is rather well extended. It prompts me to add "I should tell them how to eat and how to spare their arteries!"

THE SOCIAL AND ESTHETIC ASPECTS OF EATING

No discussion on the subject of diets for the elderly should leave out some tribute to food based on values other than its caloric content. Religious, national and family feastings on holidays have been such a civilizing influence that any campaign for better nutrition must never overlook the spiritual and social resources arising from the table or the sharing of food. While vacillating between the dangers of undereating and overeating (a fair optimum diet) I must not appear to condone the gourmand. Women are much more susceptible to food faddisms than men, and fashion is apt to dictate the basis on which many digestive neu-

roses develop. Dorothy Dix avers, apropos of woman's destiny, "They seem either to become skeletons or feather pillows." It is either a "feast or a famine" with all too many people. Prentice shows that that is history repeating itself. Hunger is a natural instinct with the young; it is often a luxury with the old. Food must be made attractive. The atmosphere should be conducive to liveliness and some approximation of what Edwin Markham calls man's primary needs: bread, brotherhood and beauty. We need a modern Brillat-Savarin¹⁶ with ability to popularize the nutritional nuggets today's science provides us in the manner in which he popularized esthetic living and dining.

PRACTICAL GUIDANCE

1. *Protein* (chapter II, Lewis).—The need of protein at all ages is now so well established that little argument need be advanced. A few simple statements for the unconvinced should suffice. Note how the "essentialness" of the amino acids keeps step with the components of B complex and B₁. I wish especially to illustrate the significance of the liver in homeostasis. Goldschmidt, Vars and Ravdin¹⁷ noted the liver protecting faculties of protein in their experiments with dogs poisoned by chloroform. Whipple's¹⁸ thesis that animal protein buffers the liver for blood plasma restoration is being augmented each month by various reports, all supporting the conclusions that protein safeguards the normal liver,¹⁹ even as dextrose (Mann and Bollman) tides over the damaged liver. Philip Brown²⁰ advises a high protein diet in ulcerative colitis in order to protect the liver. The papers by Patek²¹ and Butt

16. Brillat-Savarin, Jean Antheline: *The Physiology of Taste* (Frank Crownshield translation from original), New York, Boni and Liveright, 1926.

17. Goldschmidt, S.; Vars, H. M., and Ravdin, I. S.: *The Influence of Foodstuffs on the Susceptibility of the Liver to Injury by Chloroform and the Probable Mechanism of Their Action*, J. Clin. Investigation, **18**: 277-289 (May) 1939.

18. Whipple, George H.: *Production, Utilization and Significance of Blood Proteins*, annual lecture of the Minnesota Pathological Society, *Journal-Lancet* **59**: 482 (Nov.) 1938.

19. The liver deserves a respect comparable to the fabulous "Uncle Bim"—his resources are ever drained but never exhausted.

20. Brown, Philip W.: *Suggestions as to Diet in Certain Gastrointestinal Conditions*, University of Minnesota Continuation Course in Dietetics, Feb. 20 to 22, 1941 (page 1 of notes).

21. Patek, A. J., Jr.: *Treatment of Alcoholic Cirrhosis of the Liver with High Vitamin Therapy*, Proc. Soc. Exper. Biol. & Med. **37**: 329-330 (Nov.) 1937.

and Snell²² show the trend. Starvation edema is a matter of inadequate protein and liver efficiency. Space permitting, I could illustrate some of the follies of "arthritis," "colitis" and nondescript diets that decried the use of meat. A neglected and abused liver sets the individual toward a toppling over of his homeostasis. We may put down then, as our first duty to the aging, Teach them the importance of protein and how to get their quota, no matter how old they are, 1 Gm. per kilogram of body weight. The pellagrin and the alcoholic addict with tremens prove how dependent the brain²³ is on the liver.

Unfortunately, animal protein is expensive. Preservation and refrigeration add further costs. (Consult chapter XV, Kohman.) Those purveying food are in full accord with the present nutritional program.²⁴

TABLE 3—*Cardiovascular Deaths in Minnesota for 1940*

Total for such deaths.	7,693	
Rate per 100,000.	275.5	
60 years and over.	79.8%	
80 years and over.	24.7%	
Death certified from:		
Myocardial disease	28.4%	} 64.0%
Coronary disease	35.6%	

Utilizing the cheaper cuts of meat and making them palatable is a task for properly advised cooks, taught to develop an American goulash, but with a seasoning suitable to the American palate and without too much fat. (Consult chapter XVI, Cowgill.) We may, if harder put, learn to appreciate soy beans. It is a matter of education. It is distinctly possible to be a well fed vegetarian if milk, butter and eggs and cheese are plentiful and time is no object. Primitive peoples of our own times could teach us how the better to utilize the vitamin rich viscera. The occasional azotemic patient and the gouty, at some stage in their imbalance,

22. Butt, H. R., and Snell, A. M.: Recent Trends in Treatment of Cirrhosis of the Liver, Proc. Staff Meet., Mayo Clin. 17: 250-254 (April 22) 1942.

23. It is estimated that one person in five living beyond 65 will need segregation for mental aberrations.

24. It was announced recently that fifteen leading food dispensing corporations had established a million dollar fund with Karl Compton of the Massachusetts Institute of Technology in charge to make sure that their researches and plans were right,

should have a low protein intake; nearly every other indication, so much a part of books on diet, is a relic of a period in which attention was paid to the appearance and consistency of food and very little to its mineral, vitamin and chemical content.

2. *Fat* (consult chapter III, Bloor).—This is the food with which excess may well be dangerous, but leaving out what is needed is fatal. Burr²⁵ has demonstrated the essentialness of certain fatty acids, particularly in terms of growth, milk production in cattle and vitamin B economy. Hansen, working with him, has been able to clear up some very trying instances of eczema and dermatitis in children through feeding of certain selected fatty acids. Fat improves the taste of everything. It is the good cook's delight. For the vigorous, it invites overindulgence; even if it does not "burn in the flame of the carbohydrate" both are very compatible (as the obese well know) and energy is released without the specific dynamic action loss characteristic of protein. Fat spares all reserves, including vitamin B and protein. But when it isn't properly utilized, it clogs up the liver.

Biochemists and physiologists are baffled in attempts to trace fat through the human body and understand its interrelations with other food elements. In contrast, a lay knowledge which coined the phrase "living on the fat of the land" acclaims a great and popular appreciation of fat. The housewife chooses the beef where the muscle is well interlarded with white fat. Her husband chooses brown ties to match the gravy. For heavy work in low temperatures where much energy is expended, fat is the chief resource. Finnish woodsmen in northern Minnesota have shown me how they choose the fattest of salt pork; with amazingly sharp knives they sliced this off and sandwiched slabs of it between the bisected halves of firm, hard loaves of bread. As they took a bite through this sandwich, I was told that some with inadequate teeth used the same sharp knife to sweep the mouth free from the segment without displacing a single whisker! With copious draughts of well sweetened coffee and condensed milk, these men²⁶ could work prodigiously in subzero

25. Hansen, A. E., and Burr, G. O.: *Proc. Soc. Exper. Biol. & Med.* 30: 1201, 1933.

26. This concentrated diet was really an outpost ration: two men occupy a shack for ten days at a time, then go back to their homes.

weather, feel comfortable and maintain their weight. "How about venison?" I asked. They looked very sad and replied "No good." "Eat big hunks, just like hay." Nature herself augmenting the efforts of the game warden!

The results of Leary's rabbit experiments, in which he fed large amounts of cholesterol, have not been entirely refuted. He did prove that in the rabbit it seeped through the intima. Interest centers in the background of what cholesterol phagocytosed into the subintimal layers of the coronaries may later do in encouraging coronary inadequacy, sclerosis and thrombotic pluggage. Hurxthal,²⁷ who has given much study to the subject of cholesterol (myxedema and related states), offers no especial support to Leary's theory. From Isidore Snapper²⁸ comes a lively observation apropos of his recent experience in Japanese invaded China. He agrees with many other Occidental exchange professors who have reported from the Orient that the incidence of hypertensive disease and coronary complications is much less there than with us and implies that we have too much butter and cream at our plates. Snapper made a significant and naive observation to the effect that the very polite Chinese imparted to him the news that we Occidentals exude an unmistakable bovine aroma. Lest this be taken as a facetious implication, a recent report by Crohn and Drosd,²⁹ dealing with the mechanism whereby garlic taints the breath, showed that it is a matter of absorption and reaches the blood stream via the liver and thence to the lungs. Perhaps certain systems are surfeited with fat, and strawberry gallbladder and stones may not be the greatest insult resulting.

Recently, at a large clinical panel discussion, the question was put to Tinsley Harrison "If you had a patient with a family history of coronary disease, especially with thrombosis, would you advise the limitation of fat in the diet?" He answered affirmatively. I agree with him. Patients with gout (attacks precipitated by rich fatty foods) are very liable to coronary sclerosis.

27. Hurxthal, L. M., and Simpson, H. N.: Hypothyroidism; Hypercholesterolemia, *J. Clin. Endocrinol.* 1: 450-452 (May) 1941.

28. Snapper, Isidore: Chinese Lessons to Western Medicine, Interscience Press, 1941.

29. Crohn, Burrill B., and Drosd, Rudolph: Halitosis, *J. A. M. A.* 117: 2242 (Dec. 27) 1941.

Such clinical evidence should not be undervalued, at least until more is known about fat metabolism. It is my opinion that, if 10 per cent of the necessary calories for the inactive elderly person are derived from fat, the bodily needs will be safeguarded. Some criticism of the higher caloric intake now advised for our recruits and practiced by our athletes is heard. There is the immediate effect (weight and mobility of recruits) and the remote effect (habits of eating during forced exercise) incompatible with later sedentary lives.

3. *Carbohydrate, Vitamins and Minerals.*—Under this heading I choose to say little about their obvious virtues. I have tried to weave into this discussion a pattern that implies the great advantage of keeping nature's nutritional formulas intact; by avoiding over-refinement or processing, by getting a balanced ration and all the bodily needs will be contained therein. Age imposes certain deprivations—appetite, digestion, absorption—so that, even when a reasonable diet is consumed, certain deficiencies result. This may well occur even when obesity is present. The mouth (including the tongue, lips and fauces) has become the nutritional barometer. Ivy³⁰ states that gastric acidity slows up after 20, achlorhydria increases considerably after 40; by 65, 35 per cent of people do not secrete acid³¹ after a meal and 28 per cent show no response to histamine. Those losing their teeth (often without good reason, focal infection) frequently go through a period of adjustment to dentures when appetite slumps and subnutrition ensues. Lower plates are rarely secure. Sturdy square jawed people accommodate well to dentures, whereas neurotic and anxious individuals with natively poor bites or narrow receding mandibles find themselves unhappy. The former, with dental plates, say "These store teeth are better than my own." The latter try one dentist and denture after another. The prophylaxis for their dilemma goes back two to five decades. Is diet at fault? Weston Price³² thinks so. All nutritionists should read his book. He has gathered information from all around the world. The illustrations alone would seem to prove his thesis: native

30. Ivy, cited by Cowdry.⁵

31. Achlorhydria predisposes to decalcification, enteritis, diarrhea and general deficiencies.

32. Price, Weston A.: *Nutrition and Physical Degeneration*, New York, Paul B. Hoeber, Inc., 1939.

peoples (on the most varied source foods), when they get a balanced food and avoid overrefinement of flours and sugar excesses, bear children with properly formed jaws; the teeth are regularly spaced and both gums and teeth survive. On the contrary, as soon as they move to a region where overrefined carbohydrate in excess is available they promptly lose their teeth. The story is the same whether it concerns the cloistered group in the upper valleys of the Swiss Alps, the Hebrides Islands, African jungle tribes or our Eskimos and Indians. On the other hand, this thesis has so far little support from our leading dental colleges. Irwin³³ has collected a questionnaire from eight teachers holding professorships in basic university departments of medicine and dentistry in the United States. Five questions were posed bearing on caries and pyorrhea alveolaris, resistance thereto, the effect of diets on pregnant women, the babies' teeth, dentition and general development. Opinion or belief that diet was of little import shaded into the belief expressed by a few that nutrition was the basis of all caries and pyorrhea. I believe that this is one of the most pressing nutritional problems before us today. The lack of unanimity I mention is little short of alarming. The dental and medical professions have drifted too far apart. Harvard University's plan to remerge them is opportune.

Twenty per cent of the first draft³⁴ recruits could not qualify because of inadequate teeth. Surely something is wrong, and the best lead we have involves diets. Bleeding gums are controlled in most people by adequate citrous fruits; so-called trench mouth is an avitaminosis: when tissue dies the Vincent's organisms multiply. The deeper deprivations that come from faulty absorption from the gastrointestinal tract or from diarrheas are pathologic. At the same time we do not know to what extent the age factor produces alterations of absorption and metabolism for which it isn't feasible to get all the essential vitamin and mineral even from a diet that is adequate. There is a good field here for vitamin reinforcement.

Vitamins have not been overemphasized, but the public (at least fifty million dollars' worth of vitamin prepa-

33. Irwin, Vern D.: *Nutrition and the Teeth*, Northwest Dentistry 20: 201 (Oct.) 1941.

34. Among our families in the highest income bracket, many young girls need orthodontic adjustment of their teeth and jaws. Teeth thus pulled by braces are, in my experience, apt to be short lived.

rations was sold in the United States last year) and doctors have taken the vitamin detour to supposed nutritional sufficiency and are using various vitamin compounds as they would "bitter tonics." THE JOURNAL (through the Council on Foods and Nutrition and the Council on Industrial Health³⁵) has given a clear statement of that fallacy, and it applies in part to the field of my discussion. Among segregated groups of the elderly there is a place for evaluating the benefit of certain selected vitamins, food enforcement with scientific controls. This has been reported on by Stephenson and his co-workers³⁶ in England. There was an advantage of such enforcement. I have found many situations and reported on a few in which such utilization in the old induced a health transformation.

Closely related to the tooth problem is that of calcium and phosphorus ratios in the body. Among the elderly (women more than men) senile osteoporosis frequently is found. Albright, Smith and Richardson³⁷ have linked this up with an endocrine (internal vitamin) estrogenic deficiency. Gardner and Black have reported less dense bone shadow (x-rays) in many nervous and underfed individuals with irritable colons. Hip fractures are common and often fatal; telescoping of the vertebra (with root pains and confusion with angina) occurs after insignificant trauma. By whatever method we try to recalcify such bones, the results are discouraging. I stress this to question the use of milk as a source of calcium for old people. They do not need the fat in whole milk; skim milk is constipating if taken in large amounts and bulky foods promoting residues are left out. Cheese, buffered with vegetables, is more practical.

Water is too often neglected. Coffee and tea are preferable to chocolate, and, aside from encouraging insomnia, few suffer from their abuse. When not too strong, even in advanced years, these help greatly to keep up fluid intake. They are too often left out on rather poor excuses.

35. Indiscriminate Administration of Vitamins to Workers in Industry, Council on Foods and Nutrition and the Council on Industrial Health, J. A. M. A. 118: 618-621 (Feb. 21) 1942.

36. Stephenson, W.; Penton, C., and Korenchevsky, V.: Some Effects of Vitamins B and C on Senile Patients, Brit. M. J. 2: 839-844 (Dec. 13) 1941.

37. Albright, Fuller; Smith, Patricia H., and Richardson, Anna M.: Postmenopausal Osteoporosis; Its Clinical Features, J. A. M. A. 116: 2465-2474 (May 31) 1941.

OPERATIONS AFTER SIXTY-FIVE

Surgery for the elderly (cancer, gastrointestinal, genitourinary and central nervous system) is a test that many elderly must meet. Few prepare for it. Emergencies shorten the period of possible preparation. The medical attendant has a heavy responsibility which the surgeon should share with him. At the same time necessary surgery must not be withheld, because many of the elderly do astonishingly well even when the severest operations are done.

Wilcox and Clagett,³⁸ reporting from the general surgical sections of the Mayo Clinic for 1939 and 1940, listed 1,204 such patients over 65 operated on. The mortality was not high (8 per cent) for benign disease and operable cancer and 16 per cent for inoperable cancer and palliative operations. However, only 20 per cent (one in five) failed to have some significant postoperative complication. Naturally these were in the nature of cardiovascular insults (thrombophlebitis, embolism, pulmonary atelectasis and cerebral and kidney complications). This is what we all see within this group. What better preparation could they have had than even a fair nutritional balance? Added incentive to "keep your body as fit as you can as long as you can" arises from the great likelihood that some major operation or infection is in the offing. These operations are part of the price we shall pay for both the fuller and the longer life.

GENERAL SUMMARY OF DIETARY SUGGESTIONS
FOR THE OLD

1. Elderly people should start the day with a good breakfast.³⁹ It should include some substantial protein,* and whatever else depends on body weight and activity. Protein adequacy must be maintained at all ages.
2. As effort lessens and sedentary life supervenes, weight rise or fall should dictate the proportion of carbo-

38. Wilcox, L. E., and Clagett, O. T.: Surgical Procedures on Patients of Advanced Age, Proc. Staff Meet., Mayo Clin. 16: 75 (Dec. 10) 1941.

39. Thorn, Geo. W.; Quimby, John T., and Clinton, Marshall, Jr.: A Comparison of the Metabolic Effects of Iso-Caloric Meals of Varying Composition with Special Reference to the Prevention of Postprandial Hypoglycemic Symptoms, Annals of Internal Medicine 18: 913 (June) 1943.

* An article published since this chapter appeared in THE JOURNAL (reference 39) gives factual evidence as to the personal efficiency and comfort (absence of symptoms of hypoglycaemia) with those getting "the prolonged sense of well being which follows the ingestion of a meal rich in protein." Mid morning snacks following a meager breakfast leads to nutritional imbalances for the entire day.

hydrate taken, and as much of this as possible should be from whole grain. While bran is objectionable cracked wheat products are not. Enriching flour may be a good expedient but the objection to dark breads should be lived down. Potato is the next best starch.

3. For the obese, vegetables and fruits should act as the "fillers" and provide appetite and zest for eating by meticulous preparation and serving.

4. The elderly should eat fat sparingly, even as the middle aged should use it cautiously. The high cholesterol sources (egg yolk, cream and animal fats) should probably be curtailed wherever body build, family history and other indications portend atherosclerosis. It is the one decisive indication for dietary restriction after full stature has been attained. The danger of high blood cholesterol is not universal.

5. Tea, coffee and alcohol are useful stimulants. The abuse of alcohol places it for some people in the category of both refined carbohydrate and animal source fat. As a vasodilator it inspires as well as flushes the aged. One cannot say as much for tobacco. It soothes and cuts off circulation. The quiet postprandial puff is rapidly becoming a continuous process. Tobacco is safer after 60 than before, because age has by that time made the blood vessels less elastic and labile.

6. Food and water (hot drink) taken at regular intervals revive the old. Food becomes the best sleep producer even though early wakefulness follows. Fruit juices add the needed vitamin content.

7. Hunger lessens as age advances. Foods useless calorically (condiments, broth, relishes) have a place. The teeth, gastric acidity, probably absorptive powers, vitamin storage—all begin to fail with age. We are able to compensate for these losses with vitamins, iron, calcium, hydrochloric acid and a balanced diet. The mouth becomes the nutritional barometer of health.

CHAPTER XX

NUTRITIVE REQUIREMENTS IN PREGNANCY AND LACTATION

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The ideal normal nutritional state for pregnancy would be one in which the maternal body was endowed with the proper nutritional elements before, during and after the pregnancy, to ensure the optimum needs of the fetus in its intrauterine development, to supply stores for its needs in early infancy, to ensure adequate nutrition for the normal physiologic requirements of the mother, and for the added requirements resulting from pregnancy and lactation. It is therefore not enough to discuss the question of diet for the expectant mother by simply saying that her needs are those of any healthy woman. While we have been accustomed to thinking of the fetus as parasitic and therefore obtaining its nutritional needs even at the expense of the maternal stores, perhaps we should consider more optimum development of the fetus by making all needs readily available. Gross nutritional deficiencies are seldom encountered in the population today, but, as our knowledge of nutrition increases, more and more evidence is presented that there are minor deficiencies which impair to varying degrees the health and efficiency of our population. Such minor or subclinical deficiencies, which in the average individual would take weeks or months to develop, could be exaggerated and hastened by the increased nutritional needs during pregnancy.

To serve as a basis for discussion of the nutritive factors needed during pregnancy and lactation, without considering special obstetric problems, such as vomiting, it might be well to use table 1, which is a reproduction of the standards set by the Food and Nutrition Board of the National Research Council and adopted by the Washington National Nutrition Conference in May 1941 and by the Council on Foods and Nutrition of the American Medical Association.

DIET DURING NORMAL PREGNANCY

In order to supply the food essentials in the recommended amounts it would be necessary to provide the following foods daily in approximately the amounts specified: milk, 40 ounces ($2\frac{1}{2}$ pints); cheese, 1 ounce; butter, 2 ounces; egg, 1 serving; meat, 1 serving (liver once a week); potato, 1 serving; yellow or green leafy vegetable, such as carrots, spinach, chard, string beans, or green peas, 1 serving; vegetable such as cabbage, turnip or tomato, 1 serving; orange juice, 3 ounces, or grapefruit juice, 4 ounces, or tomato juice, 7 ounces; other fruits, 1 serving; whole grain or enriched bread, 4 slices; whole grain or restored cereal, 1 serving. Extra calories necessary would be provided in the other foods eaten in the daily diet according to the individual needs and taste. A supplement of fish liver oil or its equivalent should be prescribed to provide 400 to 800 units of vitamin D.

CALORIES

McCollum¹ states that during pregnancy there is a rise in basal metabolism which is 23 per cent higher at term than at the fourth month. The gain in weight, however, is only 14 per cent. The fetal tissues have a higher specific metabolism per unit of weight than maternal tissues. While there is increased metabolism toward the end of pregnancy, this is to some extent compensated by the necessary restriction of muscular activity during this period. The normal desirable weight gain in pregnancy according to some authorities is 20 to 25 pounds, spaced to gain 3, 10 and 10 pounds in the three trimesters.² The appetite is often diminished during the first trimester, and caloric requirements may be difficult to maintain. In the latter half of pregnancy the appetite may be increased.

FAT AND CARBOHYDRATE

Fats and carbohydrates supply the energy in the normal diet and are usually present in sufficient quantity. Their importance apart from being a source of calories, is in the absorption of vitamins by the fat and the protein sparing action of carbohydrate. The

1. McCollum, E. V.: Diet of Pregnant Woman, *Am. J. Obst. & Gynec.* 36: 586-596 (Oct.) 1938.

2. Conn, L. C.; Vant, J. R., and Malone, M. M.: Some Aspects of Maternal Nutrition, *Surg., Gynec. & Obst.* 62: 377, 1936.

ratio of carbohydrate and fat to protein and other so-called protective foods usually varies with the economic level of the family. The lower the income, the lower the intake of animal protein and vitamin containing foods.³ Obesity and excessive gain of weight during pregnancy can be controlled to a certain degree by the regulation of the intake of fat and carbohydrate.

Rucker⁴ feels that a carefully controlled diet will determine the weight of the baby. By keeping a low fluid, fat and carbohydrate intake and by increasing the protein, while keeping the total calories about 1,800 a day, he claims that the length of labor is shortened and that there is a minimum of prematurity. However, most observers feel that only gross curtailment of food intake can affect the size of the fetus. In such cases there is always the danger of some or many specific deficiencies. Garry and Stiven,⁵ in a review of the available data up to 1935, find that the weight of the newborn is not influenced by the maternal diet unless there are extreme deficiencies. This has been my experience, in which it was found that the average birth weight of babies born to a group of mothers who were given extra food during the latter months of pregnancy was 7 pounds 7 ounces, compared with an average of 7 pounds 10 ounces in a group whose mothers were left on a poor diet which was much lower in total calories.⁶

PROTEIN

Metabolism studies as reported by several workers⁷ indicate the increased requirements for protein during pregnancy and lactation. The needs of the normal

3. McCance, R. A.; Widdowson, E. M., and Verdon, C. M.: A Study of English Diets by the Individual Method: III. Pregnant Women at Different Economic Levels, *J. Hyg.* **38**: 596, 1938. Ebbs, J. H., and Moyle, W. J.: The Importance of Nutrition in the Prenatal Clinic, *J. Am. Dietet. A.* **18**: 12-15 (Jan.) 1942.

4. Rucker, M. P.: The Effect of Diet on the Outcome of Pregnancy, *Kentucky M. J.* **35**: 329, 1937.

5. Garry, R. C., and Stiven, D.: A Review of Recent Work on Dietary Requirements in Pregnancy and Lactation, with an Attempt to Assess Human Requirements, *Nutrition Abstr. & Rev.* **5**: 855-887, 1936.

7. Macie, Icie G., and Hunscher, Helen A.: An Evaluation of Maternal Nitrogen and Mineral Needs During Embryonic and Infant Development, *Am. J. Obst. & Gynec.* **27**: 878 (June) 1934. Harding, V. J., and Potter, C. T.: Excretion of "Acetone" and Nitrogen in Nausea and Vomiting of Pregnancy, *Brit. J. Exper. Path.* **4**: 105-116 (June) 1923. Hunscher, Helen A.; Donelson, Eva; Nims, Betty; Kenyon, Fanny, and Macy, Icie G.: Metabolism of Women During the Reproductive Cycle: V. Nitrogen Utilization, *J. Biol. Chem.* **99**: 507-520 (Jan.) 1933. Coons and Blunt.¹¹

6. Ebbs, J. H.; Tisdall, F. F., and Scott, W. A.: The Influence of Prenatal Diet on the Mother and Child, *J. Nutrition* **22**: 515-526 (Nov.) 1941.

nonpregnant woman of about 1 Gm. per kilogram of body weight must be increased to a total of from 90 to 125 Gm. daily in order to provide for the growth of the fetus and the uterus.

The role of protein in kidney damage and its place in the cause and course of toxemia of pregnancy are still debatable.⁸ Protein is still restricted by many in the management of toxemia, and it is believed that clinical experience supports the view that toxemia is improved or prevented by protein restriction.

Williams⁹ says that a deficiency of protein may lead to nutritional edema and tends to anemia, poor muscle tone, lowered resistance to disease and poor milk supply.

Barker¹⁰ found protein poor diets in about 50 per cent of both clinic and private patients. A condition of edema, sallow pasty complexion and puffiness of the face cleared up when his patients were put on a high protein diet.

An increase in protein in the diet tends to increase the yield of breast milk, while a decrease lowers the quantity of milk secreted.

Coons and Blunt¹¹ found that, the greater the retention of nitrogen in the last months of pregnancy, the better the chance of successful lactation.

One half of the protein in the diet should come from meat, eggs and dairy products.

CALCIUM, PHOSPHORUS AND VITAMIN D

One of the most important elements of the diet during pregnancy and lactation is calcium. With this mineral one can also link phosphorus and vitamin D. A decrease in the serum calcium in the last months of pregnancy

8. Oberst, F. W., and Plass, E. D.: Calcium, Phosphorus and Nitrogen Metabolism in Women During Second Half of Pregnancy and in Early Lactation, *Am. J. Obst. & Gynec.* **40**: 399-413 (Sept.) 1940. Strauss, M. B.: Observations on the Etiology of the Toxemias of Pregnancy: The Relation of the Nutritional Deficiency, Hypoproteinemia and Elevated Venous Pressure to Water Retention in Pregnancy, *Am. J. M. Sc.* **190**: 811-824 (Dec.) 1935. Dieckmann, W. J., and Swanson, W. W.: Dietary Requirements in Pregnancy, *Am. J. Obst. & Gynec.* **38**: 523-533 (Sept.) 1939. Dieckmann, W. J.: Comparative Studies of Blood in Nonconvulsive Toxemias of Pregnancy, *ibid.* **26**: 543-555 (Oct.) 1933.

9. Williams, P. F.: Nutrition in Pregnancy, *Am. J. Surg.* **48**: 118-124 (April) 1940.

10. Barker, M. H.: Blood Chemistry Observations in Protein Deficient and Toxic Pregnancies, *Am. J. Obst. & Gynec.* **35**: 949-953 (June) 1938.

11. Coons, Callie M., and Blunt, Katharine: Retention of Nitrogen, Calcium, Phosphorus and Magnesium by Pregnant Women, *J. Biol. Chem.* **86**: 1-16 (March) 1930.

has been shown,¹² with a return to normal after the pregnancy has terminated. In successive pregnancies with only short periods between, the serum calcium has been shown to be even lower. Mendenhall and Drake¹³ have ascribed numerous symptoms and complaints to a lack of calcium during pregnancy. They cleared up such complaints as muscle soreness, spasms, numbness, tingling and neuritis by giving calcium and viosterol to these patients.

Swanson and Iob,¹⁴ in a chemical analysis of the fetus, have shown that the calcium and phosphorus retained in the last two lunar months is 65 and 64 per cent respectively of the total body content of the full term fetus. In order to supply these needs, a daily intake of 1.5 to 2.0 Gm. of calcium is necessary.¹⁵

The relationship between calcium, phosphorus and vitamin D has been the subject of much research. It seems clear that vitamin D is related to the utilization and retention of calcium and phosphorus in the body. Vitamin D requires an adequate supply of calcium and phosphorus in order to provide a retention. In rats vitamin D causes an increased retention of calcium and phosphorus in the offspring when the diet is adequate.¹⁶ In a review by Jeans and Stearns¹⁷ it is pointed out that some persons can retain calcium in ample amounts if the intake is from 1.6 to 2.5 Gm., even without added vitamin D, but in rapidly succeeding pregnancies and periods of lactation, unless vitamin D is given there may be poor retention of calcium and phosphorus regardless of the intake.

12. Nicholas, H. O.; Johnson, H. W., and Johnston, R. A.: Diffusible Serum Calcium in Pregnancy, *Am. J. Obst. & Gynec.* **27**: 504-510 (April) 1934. Mull, J. W., and Bill, A. H.: Variations of Serum Calcium and Phosphorus During Pregnancy: I. Normal Variations, *ibid.* **27**: 510-517 (April) 1934.

13. Mendenhall, A. M., and Drake, J. C.: Calcium Deficiency in Pregnancy and Lactation: Clinical Investigation, *Am. J. Obst. & Gynec.* **27**: 800-807 (June) 1934.

14. Swanson, W. W., and Iob, L. Vivian: The Growth of Fetus and Infant as Related to Mineral Intake During Pregnancy, *Am. J. Obst. & Gynec.* **38**: 382-391 (Sept.) 1939.

15. Macy, Icie G., and Hunscher, Helen A.: An Evaluation of Maternal Nitrogen and Mineral Needs During Embryonic and Infant Development, *Am. J. Obst. & Gynec.* **27**: 878-888 (June) 1934. Oberst, F. W., and Plass, E. D.: Calcium, Phosphorus and Nitrogen Metabolism in Women During Second Half of Pregnancy and in Early Lactation, *ibid.* **40**: 399-413 (Sept.) 1940. Garry, R. C., and Stiven, D.: A Review of Recent Work on Dietary Requirements in Pregnancy and Lactation, with an Attempt to Assess Human Requirements, *Nutrition Abstr. & Rev.* **5**: 855-887 (April) 1936. Coons and Blunt.¹¹

16. Swanson, W. W., and Iob, L. Vivian: Calcium and Phosphorus Content of the Offspring After Feeding Vitamin D to the Mother Rat, *Am. J. Dis. Child.* **49**: 43-46 (Jan.) 1935.

17. Jeans, P. C., and Stearns, Genevieve: The Human Requirements of Vitamin D, *J. A. M. A.* **111**: 703-711 (Aug. 20) 1938.

That the amount of calcium and vitamin D in the mother's diet affects the density of the infant's bones and the structure of the teeth has been observed.¹⁸ Evidence has been presented to show the relation of the maternal diet to the development of rickets in the offspring. Maxwell¹⁹ has reported fetal rickets. Mellanby²⁰ has stated that calcium and vitamin D are often deficient in the mother's diet and feels that this is one of the predisposing factors in the development of rickets. Grant and Goettsch²¹ have shown a greater and earlier tendency to rickets in rats born of mothers on diets low in calcium, phosphorus and vitamin D.

Macy and her co-authors²² reported that the addition of cod liver oil and yeast to the diets of nursing mothers resulted in improved calcium assimilation and a greater feeling of well being.

The amount of vitamin D which is necessary for adult mineral metabolism is not definitely known and the amount suggested in table 1, of 400-800 units, is largely arbitrary. The administration of vitamin D in some form seems to be indicated.

In supplying the calcium in the food, the requirements for phosphorus are usually automatically supplied.

IRON

A great deal of interesting work has been published in the past few years which has given us a clearer understanding of the relation of the maternal diet to the development of anemia in the mother and the infant.

18. Toverud, K. D., and Toverud, G.: Studies on Mineral Metabolism During Pregnancy and Its Bearing on Disposition to Rickets and Dental Caries, *Acta pædiat.* **12** (Supp. 2): 1-116, 1931. Finola, G. C.; Trump, R. A., and Grimson, M.: Bone Changes in the Fetus Following the Administration of Dicalcium Phosphate and Viosterol to the Pregnant Mother, *Am. J. Obst. & Gynec.* **84**: 955-968 (Dec.) 1937.

19. Maxwell, J. P.; Hu, C. H., and Turnbull, H. M.: Fetal Rickets, *J. Path. & Bact.* **35**: 419-440 (May) 1932.

20. Mellanby, May: Diet and Teeth: III. The Effect of Diet on the Dental Structure and Disease in Man, Great Britain, Medical Research Council, Special Report Series 191, 1934.

21. Grant, A. H., and Goettsch, M.: The Nutritional Requirements of Nursing Mothers: The Effect of a Deficiency of the Antirachitic Vitamin Only in the Diet of the Mothers on the Development of Rickets in the Young, *Am. J. Hyg.* **6**: 211-227 (March) 1926. Grant, A. H.: The Nutritional Requirements of Nursing Mothers: The Effect of Lowering Both the Antirachitic Vitamin and Calcium in the Diet of the Mother on the Development of Rickets in the Young, *ibid.* **6**: 228-237 (March) 1926.

22. Macy, Icie G.; Hunscher, Helen A.; McCosh, S. S., and Nims, Betty: Metabolism of Women During the Reproductive Cycle: III. Calcium, Phosphorus and Nitrogen Utilization in Lactation Before and After Supplementing the Usual Home Diets with Cod Liver Oil and Yeast, *J. Biol. Chem.* **86**: 59-74 (March) 1930.

Studies in the anemia of rats have done much to help in the understanding of anemia in the human infant. Parsons, Hickmans and Finch²³ showed that rats fed on an iron deficient diet can rear their litters, but the second generation fed on the same diet will have diminished reproductive ability, the young will not grow properly and they will show a pronounced anemia. The hemoglobin at birth is lower in the second litter of rats on an iron deficient diet.²⁴ Murphy and Bowes²⁵ found that anemia was twice as frequent among mothers using an inadequate diet as among those using an adequate diet. Once the anemia is established, whether the so-called physiologic anemia of pregnancy or an iron deficient anemia, it is then impossible to raise the level by diet, no matter how nourishing or how much iron is available. It is therefore necessary to provide iron in such cases. Both maternal anemia and anemia of infants can be prevented by prophylactic iron therapy. Labate,²⁶ in studying three groups of women on different diets, reported that iron increased the hemoglobin whether the diet was good or not.

Neale and Hawksley²⁷ give as the cause of anemia in the mother (1) transfer of maternal reserve to fetus, (2) poor diet, (3) rapidly repeated pregnancies and twin pregnancies and (4) gastric anacidity or hypoacidity. The cause of anemia in the infant, according to Parsons and Hawksley,²⁸ is either a deficient antenatal storage of iron or a deficient postnatal supply, or both. A prime factor in this deficiency is the presence of anemia in the mother. Strauss²⁹ pointed out that anemia was present during the first year of life

23. Parsons, L. G.; Hickmans, Evelyn M., and Finch, Ethel: Studies in Anemia of Infancy and Childhood: XI. The Effect of Iron Deficient Diets on the Size of the Red Blood Cells in Rats and in the Production of Microcytic Anemia in Their Offspring, *Arch. Dis. Childhood* **12**: 369-380 (Dec.) 1937.

24. Alt, H. L.: Iron Deficiency in Pregnant Rats, *Am. J. Dis. Child.* **56**: 975-984 (Nov.) 1938.

25. Murphy, D. P., and Bowes, A. DeP.: Food Habits of Mothers of Congenitally Malformed Children: Report of 545 Families, *Am. J. Obst. & Gynec.* **37**: 460-466 (March) 1939.

26. Labate, J.: Classification and Treatment of Anemia of Pregnancy, *Am. J. Obst. & Gynec.* **38**: 48-56 (July) 1939.

27. Neale, A. V., and Hawksley, J. C.: Studies in Anemias of Infancy and Early Childhood: Nutritional Anemia in Mother and Child, *Arch. Dis. Childhood* **8**: 227-240 (Aug.) 1933.

28. Parsons, L. G., and Hawksley, J. C.: Studies in Anemias of Infancy and Early Childhood: Anhematopoietic Anemias, *Arch. Dis. Childhood* **8**: 117-144 (April) 1933.

29. Strauss, M. B.: Anemia of Infancy from Maternal Iron Deficiency in Pregnancy, *J. Clin. Investigation* **12**: 345-353 (March) 1933.

in babies born of anemic mothers although the hemoglobin was normal at birth. Mackay³⁰ showed that there was a lower level of hemoglobin in every month of the first six months of life in infants born of anemic mothers than in infants born of mothers without anemia.

The minimum requirement during pregnancy seems to be 15 mg., and according to Macy and Hunscher³¹ it may be 20 mg. daily. Corrigan and Strauss³² showed the value of supplementing the antepartum diet with medicinal iron. The results obtained in the blood of the mothers were equally striking in the blood of infants in similar studies by Gottlieb and Strean.³³

VITAMIN A

The daily requirement of vitamin A is as yet unknown, but, from various surveys and as a result of correlated dark adaptation tests, suggested requirements have been set forth. That these are far from being completely acceptable is seen when one considers the difficulties and discrepancies in the methods of measurement. The manifestation of vitamin A deficiency in any gross form is extremely rare. The incidence of minor or subclinical deficiencies is as yet unknown, but newer methods of detection may bring these to light in the near future. Again, the widespread distribution of vitamin A and its precursor carotene in our common foods suggests that it is probably not seriously deficient. However, pregnancy and lactation place extra demands on the normal physiologic processes of the female, and it is probably wise to aim at an optimum level of vitamin A and thus be within the margin of safety until our present knowledge of requirements is extended.

The part played by vitamin A in reproduction is uncertain. Mason³⁴ noted an increased rate of premature births and stillbirths in animals on vitamin A deficient diets. The young were not suckled as long

30. Mackay, H. M. M.: Nutritional Anemia in Infancy, with Special Reference to Iron Deficiency, London, His Majesty's Stationery Office, 1931 (Great Britain, Medical Research Council, Special Report Series, No. 157).

31. Macy, Icie G., and Hunscher, Helen A.: An Evaluation of Maternal Nitrogen and Mineral Needs During Embryonic and Infant Development, *Am. J. Obst. & Gynec.* **27**: 878-888 (June) 1934.

32. Corrigan, J. C., and Strauss, M. B.: Prevention of Hypochromic Anemia in Pregnancy, *J. A. M. A.* **106**: 1088-1090 (March 28) 1936.

33. Gottlieb, R., and Strean, G. J.: The Prevention of Maternal and Infant Anemia, *Surg., Gynec. & Obst.* **68**: 869-871 (May) 1939.

34. Mason, K. E.: Fetal Death, Prolonged Gestation and Difficult Parturition in Rat as a Result of Vitamin A Deficiency, *Am. J. Anat.* **57**: 303-349 (Sept.) 1935.

and lived a shorter time than normal. On the other hand, Cannon³⁵ found that congenital anomalies were not induced in the young of rats with a lack of vitamin A in the diet. They did, however, show abnormalities of pregnancy and labor as well as a tendency to sterility.

Williams, Hark and Fralin,³⁶ in observing a group of pregnant women, found 62 per cent with a low vitamin A content in an analysis of their dietary records. Only 37.5 per cent of these women had poor dark adaptation. Hirst and Shoemaker³⁷ found no significant obstetric complications among the women with vitamin A deficiencies.

Ricketts³⁸ has described severe deficiency manifestations of vitamin A simulating toxemia of pregnancy. His report deals with 2 cases.

The role of vitamin A in the development of the fetus and therefore its importance in pregnancy is strongly suggested by the work of Wolbach and Howe.³⁹ They have shown changes in the structure of the developing teeth in vitamin A deficient rats and guinea pigs. Mellanby⁴⁰ has shown defective teeth in rats born of mothers on a diet deficient in vitamin A and feels that vitamin A deficiency is responsible for absent or defective enamel and dentin.

While the newborn infant has very low stores of vitamin A,⁴¹ the colostrum and early human milk are rich in this vitamin. Human milk contains the same amount of carotene and vitamin A as cow's milk but at the beginning of lactation contains five to ten times more.

35. Cannon, M.D.: Failure of Maternal Vitamin A Depletion to Produce Congenital Anomalies in the Young of Rats, *Proc. Soc. Exper. Biol. & Med.* **44**: 129-132 (May) 1940.

36. Williams, P. F.; Hark, B., and Fralin, Florence G.: Nutrition Study in Pregnancy: Correlation Between Dietary Survey of Vitamin A Content and Dark Adaptation Time, *Am. J. Obst. & Gynec.* **40**: 1-11 (July) 1940.

37. Hirst, J. C., and Shoemaker, R. E.: Vitamin A in Pregnancy: Average Capacity According to Feldman Adaptometer, *Am. J. Obst. & Gynec.* **40**: 12-16 (July) 1940.

38. Ricketts, W. A.: Vitamin A Deficiencies in Pregnancy, *Am. J. Obst. & Gynec.* **38**: 484-488 (Sept.) 1939.

39. Wolbach, S. B., and Howe, P. R.: The Incisor Teeth of Albino Rats and Guinea Pigs in Vitamin A Deficiency and Repair, *Am. J. Path.* **9**: 275-294 (May) 1933.

40. Mellanby, Helen: Defective Tooth Structure in Young Albino Rats as a Result of Vitamin A Deficiency in the Maternal Diet, *Brit. Dent. J.* **67**: 187-194, 1939.

41. Dann, W. J.: Transmission of Vitamin A from Parents to Young in Mammals: The Vitamin and Carotenoid Contents of Human Colostrum and Milk, *Biochem. J.* **30**: 1644-1651 (Sept.) 1936.

It seems safe in our present knowledge of vitamin A requirements to believe that the requirements during pregnancy and lactation will be met by diet and the same supplement which provides vitamin D, namely 4 to 6 Gm. of cod liver oil or its equivalent.

VITAMIN B COMPLEX

Cowgill⁴² has shown that the requirement of the average person for vitamin B₁ depends on the basal metabolism and the caloric intake. Since these are increased in pregnancy and lactation, the intake of vitamin B₁, or thiamine, must be increased. Polyneuritis can occur during pregnancy,⁴³ and signs of minor deficiencies of vitamin B₁ are not uncommon. We⁴⁴ have been impressed by the changes which occurred when the intake of vitamin B₁ was doubled or trebled in women attending the antepartum clinic who had been on poor diets. Many of the minor aches and pains and numerous complaints disappeared. The mental attitude of many of these patients changed from one of apathy and discontent to one of interest in the outcome of their pregnancy. Williams and his co-workers,⁴⁵ in a nutrition study of pregnant women, found practically one third of their patients on an inadequate intake of vitamin B₁, according to the Cowgill standard. Thirty per cent of those with an inadequate intake had moderate to pronounced nausea and vomiting compared with only 10 per cent of those with an adequate intake. Fatigue, cramps, paresthesias and dyspnea were also found more frequently in those with a low vitamin B₁ intake. Strauss and McDonald⁴⁶ point out that such evidences of polyneuritis should be treated with vitamin B complex.

The need of the lactating woman for vitamin B₁ is obviously higher than for the normal nonlactating

42. Cowgill, G. R.: Human Requirements for Vitamin B₁, *J. A. M. A.* **111**: 1009-1016 (Sept. 10) 1938.

43. Neuweiler, W.: Polyneuritis During Pregnancy, *Med. Klin.* **2**: 1179, 1940; *abstr. Internat. Abstr. Surg.* **73**: 249-250 (Sept.) 1941. Allen, E.: Nutritional Requirements and Deficiencies of Pregnancy and Lactation, *S. Clin. North America* **30**: 259-268 (Feb.) 1940.

44. Ebbs, J. H.; Tisdall, F. F., and Scott, W. A.: The Influence of Prenatal Diet on the Mother and Child, *J. Nutrition* **23**: 515-526 (Nov.) 1941.

45. Williams, P. F.; Griffith, G. C., and Fralin, Florence G.: The Relation of Vitamin B₁ to the Reproductive Cycle: Correlation Between Vitamin B₁ Content of Diet and Electrocardiographic Findings in Ninety-One Pregnant Women, *Am. J. Obst. & Gynec.* **40**: 181-193 (Aug.) 1940.

46. Strauss, M. B., and McDonald, W. J.: Polyneuritis of Pregnancy: A Dietary Deficiency Disorder, *J. A. M. A.* **100**: 1320-1323 (April 29) 1932.

woman. Cowgill⁴⁷ sets this at 15 or 20 units per hundred calories, which would be 500 to 700 units daily. The amount of vitamin B₁ in the milk depends to some extent on the amount in the mother's diet.⁴⁸ There is practically no storage of this vitamin in the body. The stimulating action of B₁ on the secretion of milk has been observed.

Riboflavin, or vitamin B₂ (G), is associated with oxidation processes of the cell. With the increased metabolism during pregnancy, the requirement of this vitamin is probably increased. Forms of keratitis have been described as evidence of deficiency of this vitamin.⁴⁹ The condition described by Sebrell and Butler⁵⁰ as a result of deficiency of riboflavin has been observed in 1 patient in our own clinic.

Riboflavin is found in milk, egg white, liver and leafy vegetables in such proportions that most diets should contain a sufficient amount.

Nicotinic acid and vitamin B₆ have not been demonstrated as having any particular significance during pregnancy, except that the requirement is probably increased in proportion to those of the other vitamins.

If the diet contains an adequate amount of whole grain products, milk, meat, egg and vegetable, the components of the vitamin B complex will be supplied in sufficient amounts.

VITAMIN C

With the perfection of methods for determining vitamin C in the body, the approximate needs have been fairly clearly determined for the average woman during pregnancy and lactation. Snelling and Jackson⁵¹ in this clinic found a slight fall in the ascorbic acid level of the blood plasma toward the end of pregnancy. This and a further drop during and after labor might be explained by the decreased intake at this time and by increased needs of the fetus.

47. Cowgill, G. R.: Human Requirements for Vitamin B₁, *J. A. M. A.* **111**: 1009-1016 (Sept. 10) 1938.

48. Sure, Barnett: Influence of Massive Doses of Vitamin B₁ on Fertility and Lactation, *J. Nutrition* **18**: 187-194 (Aug.) 1939.

49. Kruse, H. D.; Sydenstricker, V. P.; Sebrell, W. H., and Cleckley, H. M.: Ocular Manifestation of Ariboflavinosis, *Pub. Health Rep.* **55**: 157-169, 1940.

50. Sebrell, W. H., and Butler, R. E.: Riboflavin Deficiency in Man: Preliminary Note, *Pub. Health Rep.* **58**: 2282-2284, 1938.

51. Snelling, C. E., and Jackson, S. H.: Blood Studies of Vitamin C During Pregnancy, Birth and Early Infancy, *J. Pediat.* **14**: 447-451 (April) 1939.

Being water soluble, vitamin C is not retained in the body and therefore the level in the blood is directly affected by the amount in the diet.⁵²

The average plasma vitamin C of two groups of women measured during pregnancy is shown in table 2. Both groups were on poor diets when the blood was first examined. One group was then given one orange and 4½ ounces of canned tomatoes daily until the end of pregnancy. It will be noted that the average level of ascorbic acid in this group was higher in the eighth month and at term than in the other group. The parasitic nature of the fetus is demonstrated by the average level of vitamin C in the cord blood, which is higher than the level in the maternal blood at this time. Even when the maternal blood was practically depleted of ascorbic acid, the cord blood would contain apprecia-

TABLE 2.—*Plasma Vitamin C During Pregnancy*

Group	5th to 6th Month Mg. per 100 Cc.	8th Month Mg. per 100 Cc.	Term Mg. per 100 Cc.	Cord Blood Mg. per 100 Cc.	Mother's Blood 6 Weeks After Delivery Mg. per 100 Cc.
Diet poor in vitamin C	0.47	0.40	0.47	1.0	0.43
Improved diet; added orange and tomato	0.46	0.69	0.73	1.4	0.38

ble though below normal amounts. The average levels in table 2 are lower than the desired level during pregnancy.

Sellig and King⁵³ have shown that the amount of vitamin C in the breast milk is dependent on the dietary intake of the mother. Totally breast fed babies are well supplied with vitamin C if the vitamin C content of breast milk is more than 4 mg. per hundred cubic centimeters. Mothers on low vitamin C diets can secrete enough vitamin C in the breast milk to give levels in the plasma of the infant which are higher than their own. While cases of scurvy in breast fed infants have been known, it is an extremely rare occurrence. Of 20 consecutive babies with scurvy admitted to the Hospital for Sick Children, Toronto, all were bottle fed.

52. Teel, H. M.; Burke, Bertha S., and Draper, Ruth: Vitamin C in Human Pregnancy and Lactation: Studies During Pregnancy, *Am. J. Dis. Child.* **56**: 1004-1010 (Nov.) 1938.

53. Sellig, Iva, and King, C. G.: The Vitamin C Content of Human Milk and Its Variation with Diet, *J. Nutrition* **11**: 599-606 (June) 1936.

It seems clear that the vitamin C intake during pregnancy and lactation should be increased above the amount usually required. Particular attention should be paid to the intake during the latter weeks of pregnancy, during lactation and during periods of vomiting or other dietary restriction. The diet should contain liberal amounts of orange, grapefruit or tomato juice as well as other fruits and vegetables.

VITAMIN E (ALPHA-TOCOPHEROL)

The need for vitamin E in normal pregnancy has been suggested recently. Reports of Vogt-Møller,⁵⁴ Currie,⁵⁵ Shute,⁵⁶ Collins⁵⁷ and Watson⁵⁸ on the use of wheat germ oil in threatened abortion have been very encouraging. Bacharach⁵⁹ summarizes some of the recent reports by suggesting that there is at least presumptive evidence that it is needed for normal pregnancy in women.

VITAMIN K

Evidence has been brought forward practically to establish the usefulness of vitamin K.⁶⁰ The administration of this substance to the mother just before the onset of labor or, failing this, during labor has a definite effect on the prothrombin time of the infant.⁶¹ A reduction in the incidence of hemorrhagic disease in the newborn period has been shown when mothers have been treated, and the use of this substance also seems to be indicated in the treatment of cases of hemorrhagic disease of the newborn.⁶²

54. Vogt-Møller, P.: Treatment of Habitual Abortion with Wheat Germ Oil (Vitamin E), *Lancet* 2: 182-183 (July 25) 1931.

55. Currie, David: Vitamin E in the Treatment of Habitual Abortion, *Brit. M. J.* 2: 1218-1219 (Dec. 18) 1937.

56. Shute, E. V.: The Early Diagnosis of Abruption Placentae and Its Treatment with Wheat Germ Oil, *Am. J. Obst. & Gynec.* 33: 429, 1937.

57. Collins, C. G.; Weed, J. C., and Collins, J. H.: The Treatment of Spontaneous, Threatened or Habitual Abortion, *Surg. Gynec. & Obst.* 70: 783-786 (April) 1940.

58. Watson, E. M., and Tew, W. P.: Wheat Germ Oil (Vitamin E) Therapy in Obstetrics, *Am. J. Obst. & Gynec.* 31: 352-358 (Feb.) 1936.

59. Bacharach, A. L.: Vitamin E and Habitual Abortion, *Brit. M. J.* 1: 890 (June 1) 1940.

60. Shettles, L. B.; Delfs, E., and Hellman, L. M.: Factors Influencing Plasma Prothrombin in the Newborn Infant: II. Antepartum and Neonatal Ingestion of Vitamin K, *Bull. Johns Hopkins Hosp.* 65: 419-426, 1939.

61. Beck, A. C.; Taylor, E. S., and Colburn, R. F.: Vitamin K Administered to the Mother During Labor as a Prophylaxis Against Hemorrhage in the Newborn Infant, *Am. J. Obst. & Gynec.* 41: 765-775, 1941.

62. Snelling, C. E., and Nelson, Winnifred: Vitamin K in Hemorrhagic Disease of the Newborn, *J. Pediat.* 17: 615-620 (Nov.) 1940

RELATION OF NUTRITION TO TEETH

Studies of the incidence and control of dental caries in the pregnant woman indicate that diet is a factor. There appears to be some truth in the old saying "For every child a tooth," and the observation has been commonly made that dental decay is increased during pregnancy.

The teeth, while requiring relatively little mineral salts in comparison to the skeleton, are nevertheless dependent on maternal supplies for their normal development. Deficiencies in the maternal stores of essential food elements, such as minerals and vitamins, will probably be reflected in the structure of the teeth of the infant. Toverud⁶³ has found defects in the teeth under such conditions, and Mellanby⁶⁴ feels that deficiencies in antepartum diet are an important factor in dental caries appearing in the child.

In observations on three groups of patients in an antepartum clinic Daro⁶⁵ found a poorer condition of the teeth and gums in those who were on inadequate diets compared to those who were eating plenty of milk, raw fruits and vegetables. He points out the importance of deficiencies which might occur as the result of vomiting early in pregnancy.

Howe⁶⁶ makes a strong point: "The dentist may and should indicate to the medical practitioner that the teeth are calcifying and the bones which carry the teeth are undergoing ossification during fetal life, and it is his duty to see that the normal processes of growth and development here go on uninterrupted. It is recognized that these processes are influenced more strongly by nutritional states than by any other factor."

While there are undoubtedly other factors in the production of dental caries, it seems reasonable that the period of development of the teeth is a most important one and the mother should be provided with the optimum requirements.

63. Toverud, K. U., and Toverud, G.: Studies on Mineral Metabolism During Pregnancy and Its Bearing on Disposition to Rickets and Dental Caries, *Acta pædiat.* 12 (supp. 2) 1: 1-116, 1931.

64. Mellanby, May: Diet and Teeth: III. The Effect of Diet on the Dental Structure and Disease in Man, Medical Research Council, Special Report Series, No. 191, London, His Majesty's Stationery Office, 1934.

65. Daro, A. F.: Dental Problems Arising During Pregnancy, *J. Am. Dent. A.* 27: 51-57, 1940.

66. Howe, P. R.: What Consideration Shall Be Given to Prenatal Care in Preparation for Good Teeth? *J. Am. Dent. A.* 26: 373-374, 1939.

NUTRITION A FACTOR IN PREGNANCY

Is nutrition a factor of importance in the management of pregnancy? This question could be answered by general statements covering the knowledge that improved nutrition improves the general health and this results in healthier mothers. Common sense and practical experience suggest the importance of proper food for the expectant mother. Poverty goes hand in hand with poor diets, but not all people with adequate incomes provide proper diets. Ignorance, illness and other circumstances also interfere with proper dietary habits.

The incidence of successful pregnancies is conceded to be better in those of good or moderate means in comparison to those who are on low income. A recent communication by Baird and Wyper⁶⁷ from Aberdeen makes such a comparison. In private specialist practice the rate for stillbirths and neonatal deaths was 12 per thousand, in hospital practice it was 54.5 per thousand and in the homes it was 78.5 per thousand live births. While there are several probable factors entering the outcome of these three classes of pregnant women, such as economic, nursing and medical, the authors say "There is thus a large wastage of child life associated with childbirth in Scotland, intimately connected with unfavorable economic conditions and malnutrition and fatigue in the mother."

Ross and his associates⁶⁸ reported that, in two groups of pregnant women, one group on a poor diet and another group on a well balanced diet, the incidence of toxemia and the levels of hemoglobin and serum protein were not significantly different. Church, Foster and Asher⁶⁹ showed that the diet of the mother was a factor in the survival of the offspring from the risks of infection.

In a recent study in this clinic⁷⁰ a group of pregnant women found to have very poor diets were divided into two groups. One group of 120 women on poor diets and

67. Baird, Dugald, and Wyper, J. F. B.: High Stillbirth and Neonatal Mortalities, *Lancet* 2: 657 (Nov. 29) 1941.

68. Ross, R. A.; Perlzweig, W. A.; Taylor, H. M.; McBryde, A.; Yates, A., and Kondritzer, A. A.: Study of Certain Dietary Factors of Possible Etiologic Significance in Toxemias of Pregnancy, *Am. J. Obst. & Gynec.* 35: 426-440 (March) 1938.

69. Church, C. F.; Foster, Claire, and Asher, Dorothy W.: Diet and Resistance to Infection: Effect of Maternal Diet, *Am. J. Pub. Health* 27: 1232-1239 (Dec.) 1937.

70. Ebbs, J. H.; Tisdall, F. F., and Scott, W. A.: The Influence of Prenatal Diet on the Mother and Child, *J. Nutrition* 22: 515-526 (Nov.) 1941.

with low incomes were followed during the last half of pregnancy as controls for 90 women on equally poor diets and low incomes who were supplied with milk, eggs, cheese, oranges, canned tomatoes, wheat germ and vitamin D capsules and who were instructed in the type of diet necessary for pregnancy. The observations made throughout pregnancy, during convalescence and on the baby showed a striking difference. The incidence of miscarriages, premature births and stillbirths, the number of infections in the mother and her general condition, both mental and physical, were much better in those who received the extra food. Changes in the blood of the mothers given extra food gave evidence that they were in a better condition during the stress of pregnancy. The general condition of the babies born of mothers who received the extra food was much better than the condition of those born of mothers who were left on their poor diets. The incidence of illness among the babies was much greater in the poor diet group.

While it is well recognized that there are many factors in the successful outcome of pregnancy, it seems reasonable that proper nutrition will ensure a more optimum general condition of the mother which will possibly prevent or at least minimize the complications that occur in pregnancy. The tired, depressed and physically poor women in this study, with a past history of a high percentage of complications, were poor obstetric risks. But even in four or five months of proper feeding this condition was greatly improved and the outcome of pregnancy was not only better than with those who were left on their poor diet but resulted in a lower rate of complications than they had experienced in previous pregnancies. This series is small and should be extended in women equally poor.

A much larger experiment was conducted in Great Britain,⁷¹ and, while the results were obtained in several districts and the experiment was not confined to one hospital, the series is so large and the results are so striking that they have some significance. Milk and egg products containing added vitamins A and D and another food rich in vitamin B were supplied during the last three months of pregnancy to needy mothers in the special areas of England and South Wales. The

71. Balfour, M. I.: Nutrition Therapy During Pregnancy, *Proc. Roy. Soc. Med.* 31: 911-914 (June) 1938.

maternal death rate in 10,384 obstetric cases in which these foods were supplied was 1.66 per thousand total births as against a rate of 6.15 among 18,854 other cases in the same districts during the same period. There was only one death from sepsis in the assisted group, as against forty-five in the nonassisted group. The number of stillbirths and neonatal deaths was 43 per cent less in the experimental group than in the nonassisted category.

SUMMARY

From the evidence presented it is apparent that the pregnant and lactating woman requires more calories, minerals, vitamins and protein than the nonpregnant woman. As shown by McCance and his associates⁷² the intake of these elements is influenced by the economic level in that "a rise in spending power led to an increased consumption of milk, fruit, vegetables and meat and a decreased consumption of bread and total cereals." They found the women on the better diets to be taller and less anemic.

The management of the nutritional needs of the expectant mother requires more care in the selection of a daily diet than does that of a normal nonpregnant woman. The increased requirements for protein, minerals and vitamins, if they are to be met by the food consumed, necessitate some instruction in most cases. This instruction can be given by the physician or by the dietitian in the clinic. Simple directions stressing the importance of eating the foods which supply the greatest amounts of the protective food elements are usually sufficient. The importance of milk, citrus fruits, green and yellow vegetables and whole grain bread and cereal are obvious. Apart from vitamin D, the requirements for the other food elements can be met by the food, provided the income is adequate.

72. McCance, R. A.; Widdowson, E. M., and Verdon-Roe, C. M.: A Study of English Diets by the Individual Method: III. Pregnant Women at Different Economic Levels, *J. Hyg.* **38**: 596-622 (Sept.) 1938.

CHAPTER XXI

ADEQUACY OF AMERICAN DIETS

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A description of the diets of a whole population can never be simple. Food habits vary from place to place and from season to season. They differ from family to family too, reflecting economic circumstances and cultural backgrounds. Even within a single family group diets of individuals vary more than is generally realized. The latter point, preserved in legend by the Mother Goose rhyme about Jack Spratt and his wife, has recently been spelled out in terms of its nutritional significance by Canadian investigators. Their studies show that among low income groups food tends to be distributed inequitably among family members.¹ As a rule, the men—the breadwinners—appear to fare best relative to nutritional needs; women and older children, worst. When there is scarcely enough to go around, mothers tend to sacrifice for other family members. Even so, however, teen age children with their high nutritional requirements often get less than enough.

Information regarding dietary levels in this country is available from two types of statistics. On the one hand are the United States Department of Agriculture's figures showing average quantities of various foods or groups of food disappearing in consumptive channels and long time trends in our nation's over-all consumption. These estimates are constructed from available data on production, imports, exports and changes in quantities in reserve (stocks) as of the beginning and the end of each year. On the other hand, there are data from numerous family dietary studies which throw much light on the extent to which various groups of the population share in these national food supplies.

TRENDS IN FOOD CONSUMPTION IN THE UNITED STATES

Per capita food supplies in this country are bountiful compared with those of most other parts of the world.

1. McHenry, E. W.: Nutrition in Canada, *Canad. Pub. Health J.* 30: 431-434 (Sept.) 1939. Hunter, George, and Pett, L. B.: A Dietary Survey in Edmonton, *ibid.* 32: 259-265 (May) 1941.

The per capita volume has remained fairly constant during the last three decades, but within the total the relative importance of various foods has shifted.² As charts 1 to 7 show, there has been a phenomenal rise in the consumption of sugar and citrus fruits, and an upward trend in the consumption of dairy products and fruits and vegetables on the whole. Paralleling these increases, there has been a decline in the consumption of potatoes, meats and grain products. From the standpoint of nutrition, certain of these trends in food consumption have enriched the diets of American people while others have impoverished them. On the credit side, for example, is the increase in consumption of dairy products, fruits and succulent vegetables; on the debit side, the increase in consumption of refined sugar. (See charts 1 to 7 from U. S. Bureau of Agricultural Economics.)

These shifts in consumption have not occurred to the same extent among all population groups. According to dietary studies made during the period 1885 to 1937,³ the decline in the consumption of grain products by village and city families has been greater among those with comparatively low food expenditures (\$1.25 to \$1.87 a week per person, 1935 retail food price levels) than among those with average and higher than average food expenditures. Among families spending less than average amounts for food, meat consumption fell to a low level in 1915-1924 and since that period has increased relatively little. In contrast, among families spending more than average amounts for food, meat consumption declined relatively more in the decade 1915-1924 but since that period has increased considerably. The rate of increase in the consumption of milk and leafy green vegetables during the last fifty years has been of about the same order of magnitude among all expenditure groups, whereas the relative increase in the consumption of vitamin C rich fruits has been more striking at lower than at higher food spending levels.

On a per capita basis, the nutritive value of the aggregate assortment of uncooked food materials estimated

2. Consumption of Agricultural Products, mimeographed releases, March, August and December, United States Department of Agriculture, Bureau of Agricultural Economics, 1941.

3. Stiebeling, Hazel K., and Coons, Callie M.: *Present-Day Diets in the United States*, in *Food and Life*, Yearbook of Agriculture, 1939, Washington, D. C., Government Printing Office, 1940.

as delivered to the nation's kitchens during the two periods 1920-1924 and 1936-1940 is compared in certain respects with the dietary recommendations announced at the 1941 National Nutrition Conference for Defense by the National Research Council's Food and Nutrition Board⁴ (table 1). It would appear that diets in this country could meet the recommendations for nutrients

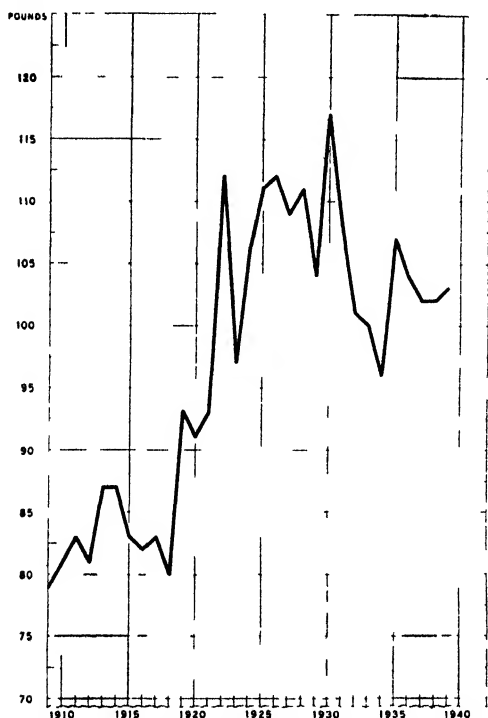


Chart 1—Per capita consumption of cane and beet sugar, raw basis, in the United States, 1909-1939.

listed except in the case of calcium, riboflavin and thiamine (on a per hundred calory basis), provided the food was distributed equitably among the population.

The figures presented on nutritive content of our food supply tend to be high, however. They refer

4. Recommended Dietary Allowances, Committee on Food and Nutrition, National Research Council (May) 1941, Distributed by Federal Security Agency, Washington, D. C.

to food brought into the kitchen and take insufficient account of the losses of nutrients in the preparation of food and of the edible food waste. Only average quantities of inedible refuse were deducted. In contrast, the dietary recommendations of the National Research Council's board with which the nutritive values of food supplies are compared represent actual intake and do not make allowances for losses in cooking. Hence, the over-all picture drawn of dietary

TABLE 1.—*Comparison of Nutritive Value of Food Estimated to Be Delivered to Nation's Kitchens in Two Five Year Periods with 1941 Dietary Recommendations of National Research Council's Food and Nutrition Board*

Nutrient	Nutritive Value per Capita per Day of Total Food Delivered to Kitchens * in		Per Capita Allowances † Based on 1941 Recommendations of National Research Council's Food and Nutrition Board
	1920-1924	1936-1940	
Food energy, calories.....	3,280	3,220	2,800
Protein, Gm.....	84	82	66
Calcium, Gm.....	0.77	0.82	0.9
Iron, mg.....	14	14	12
Vitamin A value, international units	4,900	6,000	4,700
Riboflavin, mg.....	1.7	1.8	2.3
Thiamine, total, mg.....	1.7	1.7	1.6
Thiamine, per 100 calories, mg.....	0.05	0.05	0.057
Ascorbic acid, mg.....	80	90	70

* Computations based on unpublished data on consumption, supplied by O. V. Wells, Bureau of Agricultural Economics.

† Allowances suggested by the committee for seventeen age-sex-activity groups were weighted by the number of persons in each group as judged from the 1940 census of population.

adequacy tends to be optimistic. Nevertheless, the differences between the two five year periods probably are reliable—little change in the nutritive value of diets with respect to food energy, protein, iron and most of the B vitamins but an upward trend in calcium, vitamin A value and ascorbic acid.

SOME FACTORS AFFECTING FOOD CONSUMPTION LEVELS

Averages for the country as a whole are useful chiefly as a background against which to discuss variations in consumption. The generous food supplies enjoyed

by some families bring up national averages but confer no benefit on those having but meager resources. Dietary studies show that within a population families in the upper income classes tend to have a greater variety and abundance of food than their less prosperous neighbors. However, at each income level the larger the family the less ample the diet of each person tends

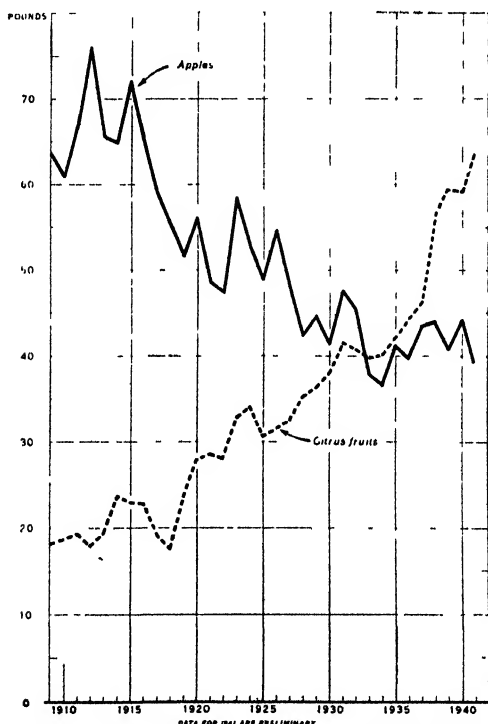


Chart 2.—Per capita consumption of fresh apples and citrus fruits in the United States, 1909-1941.

to be. Furthermore, there are wide variations in nutritive quality of diets even among those having equal economic resources, owing to differences in managerial ability and knowledge and skill in food selection and preparation.

This section of the paper will be confined to variations in diet reflecting differences in income, family size and management practices, with some comparison of

farm and nonfarm situations. These appear to be among the most significant, though by no means the only, factors affecting family dietary levels. Most of the illustrations are taken from reports of large scale dietary studies made by federal agencies in 1936.⁵

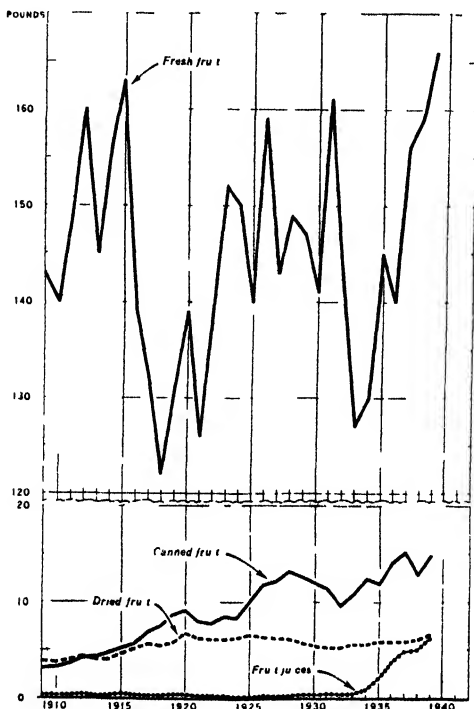


Chart 3 Per capita consumption of fruits in the United States, 1909-1939

DIET IN RELATION TO INCOME

Comparatively little difference from one income class to another was found in 1936 in per capita consumption of grain products, of fats and, in villages and cities, of sugar. On farms there appeared to be some increase in sugar consumption as incomes rose. Both in villages and cities and on farms there were moderate

5. Family Expenditures in Selected Cities, 1935-36, Food, bulletin 648, vol. 2, United States Department of Labor, Bureau of Labor Statistics, 1940 Stiebeling and her associates.⁶

increases in the consumption of milk, eggs and meat at successively higher income levels, with the rate of increase about the same for all of these groups of products. Of fruits and vegetables (other than potatoes and dried beans and peas) there was a decided increase in the quantities consumed as incomes went up. In general, however, the rate of increase in con-

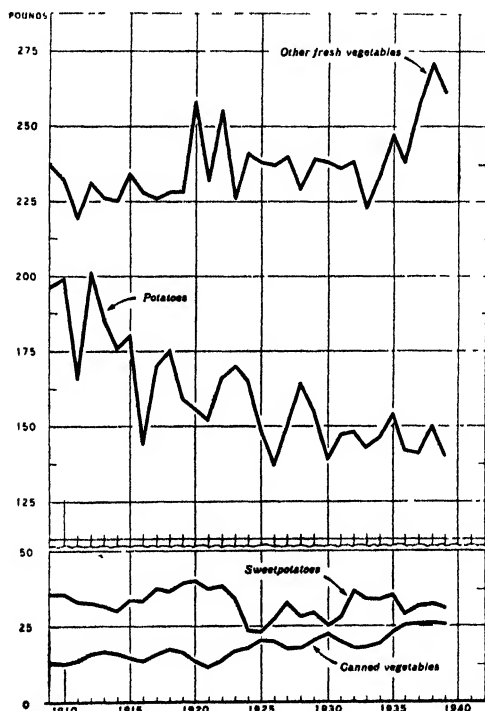


Chart 4.—Per capita consumption of vegetables in the United States, 1909-1939.

sumption accompanying successively higher incomes was greater in the lower ranges of the income scale—e. g., under \$1,500 a year—than in the upper. Table 2 illustrates these points.

As would be expected from such trends in consumption, diets of higher income groups tend to provide more protein, minerals and vitamins than those of low income groups, both absolutely and relatively to caloric

TABLE 2.—*Per Capita Food Consumption, Farm and Village and City Families in the United States: Estimate of Average Quantities Consumed of Eleven Food Groups per Year, by Income Class, 1935-1936**

Income Class	Milk (or Its Equiva- lent), Quarts	Potatoes, Sweet Potatoes, Pounds	Dry Beans, Peas, Nuts, Pounds	Tomatoes, Citrus Fruits, Pounds	Leafy, Green, Yellow Vege- tables, Pounds	Other Vegetables and Fruits, Pounds	Eggs, Dozen	Lean Meat, Poultry, Fish, Pounds	Flour, Cereals, (Baked Goods EQUIVA- lent), Pounds	Fats (Including Butter, Bacon, Salt Side), Pounds	Sugars, Syrups, Preserves, Pounds
Farm families											
All incomes.....	226	159	16	43	57	152	23	102	255	70	52
Under \$500.....	177	97	14	27	49	135	16	73	274	60	68
\$500 to \$999.....	217	131	14	36	54	138	20	84	265	71	77
\$1,000 to \$1,499.....	241	198	18	49	59	150	26	117	241	70	89
\$1,500 to \$1,999.....	264	209	16	53	64	163	31	130	236	69	92
\$2,000 to \$2,999.....	282	233	16	66	71	193	34	148	226	71	102
\$3,000 to \$4,999.....	278	270	21	75	78	201	34	168	247	84	108
\$5,000 or over.....	321	252	26	94	51	200	36	172	249	89	105
Village and city families											
All incomes.....	161	116	10	101	73	220	23	130	177	60	68
Under \$500.....	84	85	10	31	41	106	15	69	223	61	64
\$500 to \$999.....	136	117	12	68	58	164	21	105	172	57	65
\$1,000 to \$1,499.....	173	119	10	96	72	210	24	127	167	58	69
\$1,500 to \$1,999.....	179	122	11	117	82	247	26	143	167	61	69
\$2,000 to \$2,999.....	196	124	9	142	91	286	28	160	171	63	71
\$3,000 to \$4,999.....	210	124	8	174	102	341	29	185	167	66	72
\$5,000 or over.....	242	133	10	240	127	498	32	262	200	78	82
All families											
All incomes.....	177	127	11	87	69	293	23	123	196	62	71

* Data from Consumer Purchases Study (Stiebeling and her associates;^a Stiebeling ⁷), adjusted for seasonal consumption and for food eaten away from home.

value. The nutrients with respect to which diets of low and high income groups differ most widely are calcium, vitamin A, ascorbic acid and riboflavin.

Farm family diets differ from those of village and city dwellers in a number of respects. At comparable income levels farm groups consume per capita decidedly more of the important energy yielding foods—grain

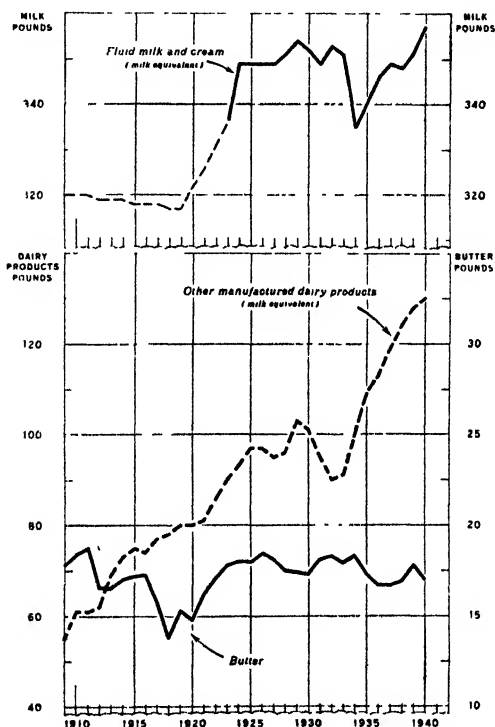


Chart 5.—Per capita consumption of dairy products in the United States, 1909-1940.

products, potatoes, mature beans and peas, sugars and fats, reflecting perhaps the heavier manual work, longer hours of toil and probably greater exposure to weather. Farm families consume more milk too. This is due, in part, to the fact that cows are milked on about three fourths of the farms in this country. Milk, then, is available for use by many families without direct cash outlay, and hence there are fewer economic bar-

riers to its use. Furthermore, on farms there are more children per family than in urban areas. The census of 1940 showed that of every hundred persons on rural farms there were 32 persons under 15 years as contrasted with 22 in cities.

Farm families do not consume more than city groups of all kinds of food, however. In general, on a per capita basis, they tend to eat less meat, poultry and

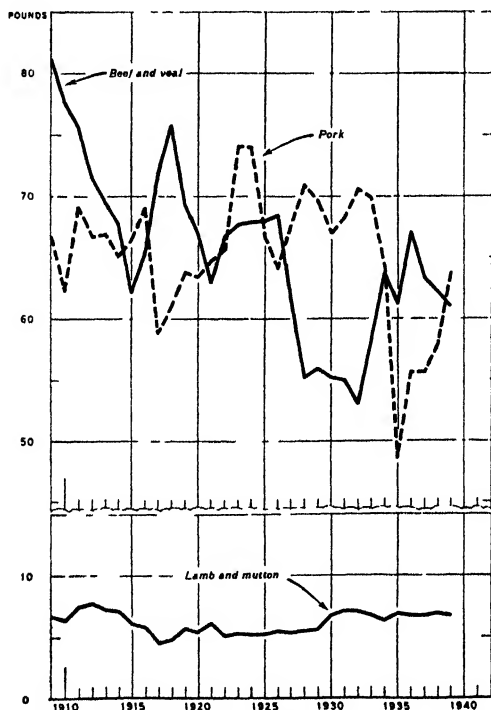


Chart 6.—Per capita consumption of meats in the United States, 1909-1939.

fish and less fruit and vegetables (other than potatoes and mature beans and peas).

Knowledge is still too incomplete to make possible a thoroughgoing appraisal of the nutritive adequacy of the diets of this nation. There is need for more information regarding both nutritive values of food as commonly eaten and human nutritional needs. But a provisional picture of the nutritive quality of diets

of various population groups can come from the Bureau of Home Economics classification of family dietary records by their nutritive content.⁶

On the basis of these studies tentative estimates for 1936 indicate that about one fourth of the families in this country had diets that could be rated good, more

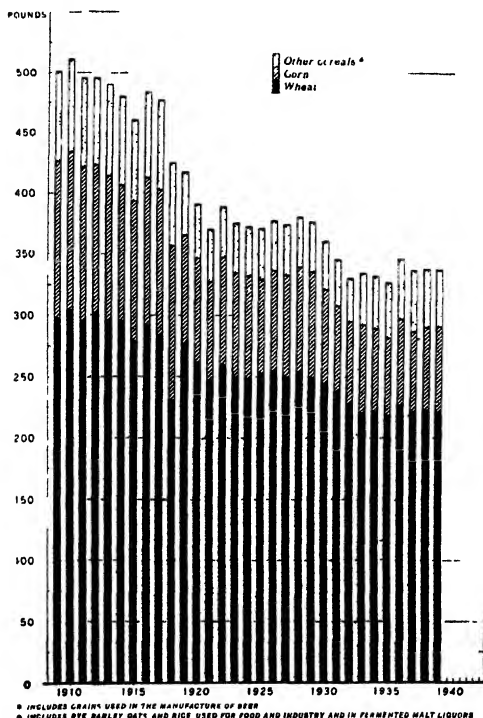


Chart 7.—Per capita consumption of wheat, corn and other cereals for food in the United States, 1909-1939. This includes grains used in the manufacture of beer. Other cereals include rye, barley, oats and rice used for food and industry and in fermented malt liquors.

than a third diets that could be considered fair and another third diets that should be classed as poor.⁷

6. Stiebeling, Hazel K.; Monroe, Day; Coons, Callie M.; Phipard, Esther F., and Clark, Faith: *Family Food Consumption and Dietary Levels, Five Regions*, Farm Series, miscellaneous publication 405, United States Department of Agriculture, 1941. Stiebeling, Hazel K.; Monroe, Day; Phipard, Esther F.; Adelson, Sadye F., and Clark, Faith: *Family Food Consumption and Dietary Levels, Five Regions, Urban and Village Series*, Miscellaneous publication 452, United States Department of Agriculture, 1942.

7. Stiebeling, Hazel K.: *Are We Well Fed?* Miscellaneous publication 430, United States Department of Agriculture, 1941.

Recently the food records from these studies have been reclassified by separating from those formerly called good the ones that provided the several nutrients in the quantities recommended in 1941 by the National Research Council's Food and Nutrition Board. In this paper these diets of higher nutritive value have been labeled excellent. Considerably fewer than a fourth of the nation's families in 1936 would have been in the excellent diet category.

At successively higher incomes there generally is found an increasing proportion of families with diets that could be graded excellent. This follows from the larger quantities of milk, butter, meat, eggs, succulent vegetables and fresh fruits usually found in the more expensive diets. Chart 8 shows the proportion of families at different income levels with diets classed as excellent, fair or good. (The chart is based on food records obtained in 1936 from village and city families of parents and one or two children living in the North and West.) In the income class \$500-\$999, about 10 per cent had excellent diets; in the class \$3,000 and over, 40 per cent.

Both on farms and in villages and cities, family diets vary in their richness with respect to different nutrients at any given level of food expenditure. Take, for example, diets of families in the North and West with food worth 30 to 40 cents a day per man—a not uncommon level of food expenditure in 1936. About 70 per cent of the village and city families in this population group had food that provided less calcium than that recommended by the Food and Nutrition Board. Thirty per cent had less vitamin A, 70 per cent less ascorbic acid and 75 per cent less riboflavin. On farms, 30 per cent of families with food valued at 30 to 40 cents a day per man had diets providing less than the recommended quantities of calcium, 20 per cent less of vitamin A, 60 per cent less of ascorbic acid and 40 per cent less of riboflavin. (Because farm furnished food was valued at less than urban retail prices, a given sum represents a greater total volume of food among farm than among nonfarm groups; this fact as well as characteristic differences in diets, discussed earlier, accounts for the differences in nutritive value just noted.)

No one should assume that all families with diets falling short of desirable goals suffer from obvious nutritional deficiencies. But the diets of many such families are amenable to improvement, the degree dependent on the extent to which the diet falls short of optimum. Many diets that are "passable" in the sense that their nutritive quality is not questioned by the general public cannot be considered satisfactory by the scientist with an insight into the contributions that food at its best can make to the well-being of the individual and the race.

Food plays an important part in determining the composition of body tissues and the fluids that bathe

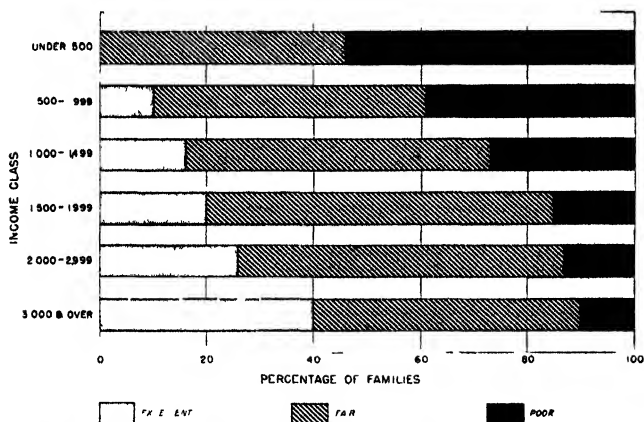


Chart 8.—Percentage of families in various income classes having diets of specified nutritive value. Dotted area indicates excellent, diagonal lines, fair; black, poor.

the cells, forming what Sherman calls the "internal environment" in which life itself goes on.⁸ Differences in this environment, many of which may be too small to be measured by present methods, definitely affect the plane on which physical and mental functioning go on. As far as the immediate or long term well-being of a person can be improved through dietary betterment, that person falls short of being truly well fed.

A nationwide study has not been made of the prevalence of inferior nutritional status. Were one to mea-

8. Sherman, H. C.: *Some Aspects of the Present Significance of Nutrition*, J. Franklin Institute 231: 305-321 (April) 1941.

sure the incidence of malnutrition in the United States merely by the number of death certificates that list malnutrition as a primary cause, the country would appear to be singularly free from this reproach. In recent years considerable progress has been made in developing technics for measuring nutritive status and revealing incipient malnutrition through biochemical or physiologic tests. Viewed broadly, the results of such studies support conclusions derived from an appraisal of diets of various population groups. To cite from but one—a study made recently in New York City comparing the nutritive status of children in a school serving chiefly families of the lower income group with those in a private school patronized by the more well to do:⁹ In the low income group more than three fourths of the city children examined showed some stage of avitaminosis A, three fourths some degree of ariboflavinosis and one half plasma levels of ascorbic acid below 0.6 mg. per hundred cubic centimeters. In the high income group less than 3 per cent of the children showed mild ariboflavinosis and less than 6 per cent had ascorbic acid levels below 0.6 mg. per hundred cubic centimeters. Studies in other communities also show differences in nutritive status associated with dietary differences characteristic of various economic groups.

9. Wiehl, Dorothy G., and Kruse, H. D.: Medical Evaluation of Nutritional Status: V. Prevalence of Deficiency Diseases in Their Sub-clinical State, *Milbank Memorial Fund Quarterly* **19**: 241-251 (July) 1941. Hunt, Eleanor P.: VI. Dark Adaptation of High School Children at Different Income Levels, *ibid.* **19**: 252-281 (July) 1941. Crane, Marian M.; Woods, P. W.; Waters, E. M., and Murphy, E. F.: A Study of Vitamin C Nutrition in a Group of School Children, *Proc. Am. Inst. Nutrition, J. Nutrition* **10**: 16 (June) 1940. Zayaz, Stella L.; Mack, Pauline Berry; Sprague, Phyllis K., and Bauman, A. W.: Nutritional Status of School Children in a Small Industrial Area, *Child Development* **11**: 1-25 (March) 1940. *Milbank Memorial Fund, New York: The Changing Front of Health, Proc. 18th Ann. Conf. of Milbank Mem. Fund, 1940.* Goldberger, Joseph; Wheeler, C. A.; Sydenstricker, Edgar, and King, W. J.: A Study of Endemic Pellagra in Some Cotton Mill Villages of South Carolina, *United States Public Health Service Hygienic Laboratory, bulletin* 153, 1929. Jeness, Rachel N.: Gain in Weight and Its Association with Ancestry and Economic Status, *Human Biology* **12**: 532-544 (Dec.) 1940. Sandels, Margaret R.; Cate, Helen D.; Wilkinson, Kathleen P., and Graves, L. J.: Follicular Conjunctivitis in School Children as an Expression of Vitamin A Deficiency, *Am. J. Dis. Child.* **62**: 101-114 (July) 1941. Milam, D. F., and Wilkins, W.: Plasma Vitamin C Levels in a Group of Children Before and After Dietetic Adjustment, *Am. J. Trop. Med.* **21**: 487-491 (May) 1941. Ebbs, J. H.; Tisdall, F. F., and Scott, W. A.: The Influence of Prenatal Diet on the Mother and Child, *J. Nutrition* **22**: 515-526 (Nov.) 1941. Kooser, J. H., and Blankenhorn, M. A.: Pellagra and the Public Health: A Dietary Survey of Kentucky Mountain Folk in Pellagrous and in Nonpellagrous Communities, *J. A. M. A.* **116**: 912-915 (March 8) 1941.

DIET IN RELATION TO SIZE OF FAMILY
AND INCOME

The size of the family as well as its income determines how much money may be spent for the food of each person. For example, in small North Central cities in 1935-1936, families of two persons with incomes of \$500 to \$750 spent an average of about 11 cents a meal per person. When there were four in the family, it seemed to take incomes of \$1,250 to \$1,500 to afford approximately 11 cent meals; and with five or six in the family, incomes of \$2,000 to \$2,250.¹⁰ While the larger sized family can effect some economies in the purchase of food as well as in its preparation, these economies seldom compensate for the progressive reductions in average food expenditures per person made within an income class by groups of families progressively larger in average size. In general, within an income class, the larger the family the less money is available for the food of each person and therefore the smaller the quantities of protective food bought for each person and the smaller the proportion of families with diets that can be classed as excellent.

DIET IN RELATION TO MANAGEMENT PRACTICES

At every level of money value of food, some families succeed in obtaining better diets than others. Granted that there are minimum expenditures below which fully adequate diets cannot be purchased and that increases in economic resources simplify the matter of obtaining satisfactory meals, it should be noted that even liberal expenditures for food do not guarantee adequate diets. The homemaker who is a good manager and a good cook, who keeps up to date on food values and nutrition and applies this knowledge to her meal planning is likely to keep her family well fed. She knows how to buy food economically, to prepare it appetizingly and to serve it attractively. Without such skills and thrift in market and kitchen, a family may be aware of the importance of good nutrition but be unable to achieve it within the limits of its resources.

Families in the higher income classes are somewhat more likely to buy satisfactory diets than those with

10. Brady, Dorothy S.; Monroe, Day; Phelps, Elizabeth, and Rainboth, Edith D.: *Family Income and Expenditures, Five Regions: Part 2, Family Expenditures, Urban and Village Series*, miscellaneous publication 396, United States Department of Agriculture, 1940.

more limited economic resources, even with the same expenditures for food. Not only do family members in the higher income classes usually have the advantage of a longer period of formal education, but they are the more likely to have radios and periodicals that bring up to date nutrition information, including facts regarding food requirements, food values and selection and wise food preparation. In addition, they are more likely to have the resources and storage space that are needed for buying food on a relatively large scale. The hand to mouth or meal by meal buying that many low income families resort to is, of course, a relatively expensive practice.

Farm families face additional problems in safeguarding the nutritive quality of diets. Most of them must raise a substantial share of their food supply if they are to be well fed. This requires labor. It requires land for food and feed and capital for investment in cows, pigs, chickens and farm equipment for production. It requires managerial ability in planning ahead for months and even years. It requires knowledge and skill for production and conservation of food. It requires courage when weather hazards or uncontrollable insect pests bring ruin to months of work. But well planned home food production programs enable farm families in many communities to enjoy diets of enhanced nutritive value.

A dollar's worth of milk, eggs, meats, vegetables and fruits from the farm (valued at prices farmers would pay if they bought them from neighbors) represents much higher returns in the nutritive essentials than a dollar's worth of staple products such as white flour, lard, sugar and coffee bought at the retail food store. Dietary studies among farm groups have shown that within a given income class, especially at the lower range of the income scale, adequacy of diet depends much less on the cash spent for food than on the quantity and variety of farm furnished food. Of course, highest returns for productive effort will come if planning—with human needs in mind—precedes the work of production. Agencies working to help farm families improve their living levels have placed increasing emphasis on planning ahead for the production and purchase of an adequate family food supply on a year round basis.

THE DIETARY SITUATION IN THE EARLY 1940'S
AS COMPARED WITH THE MIDDLE 1930'S

There are reasons to believe that diets in the United States were better in 1940 and 1941 than five years earlier. Many families had higher incomes and could buy more and better food. With the acceleration of the defense program, many unemployed got jobs, WPA employed workers got better jobs, part time workers got full time employment, and some workers in defense industries got higher wages. Food prices were at a low level in 1940 and early 1941, so that despite the rises in the cost of food during the latter part of 1941 incomes of wage earners bought more food in both 1940 and 1941 than five years earlier. Indeed, it seems possible that, with their increased power to buy, at least one family out of every seven that had had poor diets in 1936 was able to obtain a fair or good diet in 1941.

Public interest in food has been on the increase for many years, thanks to the cumulative effect of sound educational programs. The National Nutrition Conference for Defense called by the President in 1941 highlighted the subject so that it has become the focal point for the research, teaching and action programs of an increasing number of persons, groups and agencies. Following this conference there has been renewed interest in establishing state and local nutrition committees whose function it is to integrate the work of all groups that impinge on the problem of better diets. This action has greatly stimulated the demand for simple educational material and effective methods to help families redirect their dietary habits and to revamp their management practices for the sake of improving dietary levels.

Public interest in nutrition also has led to growing concern regarding the nutritive value of common foods and the effect of processing on them. On the recommendation of the National Research Council's Food and Nutrition Board, millers and bakers began in 1941 to put on the market an "enriched" white flour and bread, thereby contributing to the thiamine, nicotinic acid and iron content of diets of families customarily consuming large quantities of these products (W. F. A. Order No. 1). Canadian and British scientists and policy makers have recommended that flour in

those countries be milled somewhat less highly, so that more of the vitamin and mineral content of the original berry is retained, thus securing without "restoration" a product much more nutritious than patent flour.

The manufacture of vitamin concentrates and the production of synthetic vitamins have been stepped up greatly during the last few years. These special foods can play a useful role in dietary reinforcement, although their indiscriminate use often wastes money which might better be spent for ordinary food.

Contributing directly to dietary improvement for several years were the several food distribution programs of the United States Department of Agriculture. The food stamp program, direct distribution, school lunches and arrangements for low priced milk helped channel an enlarged share of national food supplies to needy persons.¹¹ As a result, almost 175 million dollars' worth of additional food was made available to the underprivileged in 1940-1941. Although this amount was small compared to the total food bill of the country, the programs were of very great importance to the participants.

In 1940-1941 a monthly average of 8.8 million persons in family groups received foods made available

11. The food stamp program was operating early in 1942 in areas containing more than half of the nation's population. Blue stamps, given under certain arrangements to public aid families, served to increase by about 50 per cent the food buying power of those taking part in the program. Commodities designated by the Secretary of Agriculture were available at local stores in exchange for the blue stamps. Blue stamp foods listed during January 1942, for example, included eggs, butter, pork, fresh pears, apples, oranges, grapefruit, fresh vegetables including potatoes, dried prunes, dry beans, corn meal, hominy (corn) grits and various forms of wheat flour.

Where the food stamp program was not in operation, commodities bought by the Surplus Marketing Administration under programs designed to strengthen farm markets were distributed by welfare agencies to public aid families. The supplies so distributed are in addition to what these needy families are able to buy or otherwise obtain.

Increasing quantities of food were being distributed for use in school lunch programs for needy children. The lunches may be made in whole or in part from the commodities supplied by the Surplus Marketing Administration. In most places foods needed to round out the meals were supplied by the local community groups sponsoring the program in the schools.

Greater consumption of fluid milk was being encouraged among underprivileged families by low priced milk programs. These were of two types—one supplied milk to public aid families at a low price and the other made milk available for use by school children at a penny a half pint. The low price at which the milk was supplied to eligible persons was made possible through provision for a special price to be paid producers, and through a federal indemnity payment to handlers whose bids for furnishing the milk were accepted. The indemnity payment, plus the price received from sales, reimbursed each handler for the milk and the handling and distributing services. The special producer price paid for milk used in the programs was lower than that for regularly sold fluid milk but higher than the price producers receive for so-called surplus milk used for manufacturing purposes.

under the direct distribution program, and an average of 2.9 million persons a month participated in the food stamp program. The school lunch program reached an average of 2.9 million children a month during the year (4.7 million in March, the peak month). Under the penny milk program, more than 900,000 children in eight cities, principally New York, purchased nearly 12 million quarts of milk. About 460,000 persons in family groups in six cities participated in low priced milk programs, purchasing 68 million quarts.¹²

As far as studies have been made¹³ it seems clear that participants in these programs had better balanced as well as more abundant diets than nonparticipants of equal economic status. Something of the variety of the foods made available through the programs is indicated by the following list: butter, eggs, pork, lard, potatoes, other fresh vegetables, dry beans, rice, corn meal, wheat flour (white and whole wheat), oranges, grapefruit, apples and prunes. All these foods were bought in comparatively large quantities with blue stamps in 1940. (The list of foods available under the several programs varies from month to month.) These foods were not merely superimposed on supplies that would normally be purchased. Participating families follow the procedure of farm families—modifying their usual purchases somewhat, the better to complement those obtained without direct outlay.

Both the school lunch and food stamp program in 1940 reinforced the diets of participants in many directions, but especially with respect to vitamin A, thiamine and ascorbic acid. Food obtained directly through the program contributed little, however, to correcting the frequently recurring shortages of calcium and riboflavin. The fact that the programs were in operation, however, contributed to this end. For example, studies have shown that stamp plan participants bought more milk than comparable nonparticipants (milk is an eco-

12. Surplus Marketing Administration, Monthly Reports, United States Department of Agriculture.

13. Gold, N. L.; Hoffman, A. C., and Waugh, F. V.: Economic Analysis of the Food Stamp Plan; A Special Report, United States Department of Agriculture, 1940. Southworth, H. M., and Klayman, M. I.: The School Lunch Program and Agricultural Surplus Disposal, miscellaneous publication 467, United States Department of Agriculture, 1941. Stiebeling, Hazel K.; Adelson, Sadye, F., and Blake, Ennis C.: The Effect of a Low Priced Milk Program on the Consumption of Dairy Products Among Certain Groups of Low Income Families, Washington, D. C., 1940, circular 645, United States Department of Agriculture, 1942.

nomical source both of calcium and riboflavin, among other nutrients). Furthermore, sponsors of school lunches in many communities provided milk to supplement meals that could be prepared from foods furnished by the Surplus Marketing Administration.

The two government aided milk programs directly encouraging milk consumption among needy families were on a small scale in 1940. That families will greatly increase their purchases of milk when it is available at a low price is illustrated by figures from a study made in Washington, D. C.: Before the program was begun white participants consumed milk in all forms (fluid or evaporated or in the form of cheese or ice cream) in quantities equivalent in nonfat milk solids to 2.50 quarts of fluid milk a week per person and to 4.06 quarts after the program went into effect; among Negro families, the average quantity was equivalent to 1.89 quarts a week per person during the preprogram study, compared with 3.48 quarts afterward.

It is difficult to estimate the net effect on dietary levels of any public aid food distribution programs. How much the nutritive value of the customary diets of families on relief is improved depends on many things, including the usual food consumption of families before their participation in the program, the variety and quantity of foods purchasable or distributed through the programs and the adjustments in usual diet patterns that families make because of the foods available under the program.

Over-all per capita consumption of many foods was higher in 1940 and 1941 than in 1936 as a result of the combined influence of educational programs, increased power of consumers to buy, food distribution programs and more abundant food supplies. Gains were greatest in fruit and fresh vegetables. Consumption of fresh citrus fruit was more than a third higher—other fruit and fresh vegetables between 10 and 15 per cent higher. Consumption of meat and eggs was 8 to 10 per cent higher, but of dairy products less than 5 per cent higher. There was a slight decrease in the quantities of grain products and potatoes. These shifts probably have meant considerable increases in the ascorbic acid content of American diets and some increase in the consumption of protein, thiamine and riboflavin.

To provide the nutrients in quantities and proportions recommended by the National Research Council's Food and Nutrition Board, the Bureau of Home Economics has evolved a number of plans for market lists at various cost levels.¹⁴ These market lists are in terms general enough to be followed in any part of the country. If every one in the United States should follow such plans and thus redirect dietary habits, 1936 levels of consumption for the country as a whole would be increased by at least 50 per cent in milk and by at least 50 to 100 per cent in vitamin C rich fruits and the nutritionally important leafy, green and yellow vegetables. The increases in the consumption of milk in its various forms—skim milk, fluid and dry, cheeses and evaporated milk as well as whole fluid milk—would help enrich diets in both calcium and riboflavin. At the present time too large a proportion of our skim milk—a product that supplies all the nutrients of milk below the cream line—is used in animal feed rather than for human consumption.

Whether in the war years the dietary gains of the early forties can be maintained or accelerated and improvements in still other directions initiated, time alone will tell. Enormous quantities of food are needed for our own civilian population and armed forces and for those of other countries resisting aggression. Unless enough food and food of the right kind is produced and equitably distributed dietary levels will fall.

Whether the nutritional gains of the 40's can be maintained or accelerated during the war period and improvement in diets be accomplished in still other directions remains to be seen. Public and private groups and many individuals are directing much energy to this end, but enormous quantities of food are needed for the civilian population and armed forces of this country, for those of the United Nations, and for the relief and rehabilitation of populations as they are liberated from Axis control. Food has become a powerful weapon of war.

In 1942 the shipping situation cut short the supplies of sugar and coffee in this country and necessitated economy in the use of fats, but the needed restrictive

14. Three market lists for low cost meals, and market lists for moderate cost and liberal meals, Bureau of Home Economics, United States Department of Agriculture, 1941.

measures caused no anxiety for the nutritional welfare of this country. In 1943 there was a great increase in the ability of many people to buy. This, together with a reduction of market supplies of many civilian goods such as automobiles and household equipment and furnishings, increased greatly the market demand for food. As a result, processed foods, meats, and fats were rationed to help equalize distribution.

We may expect to continue to share our food supplies for some time to come and in the meanwhile we may be called upon to learn to use more of some foods to which we are but little accustomed; but whatever lies ahead, all of us as consumers can make a real contribution to dietary adequacy in this country if we will make every effort to use food wisely by avoiding waste and by bringing our food habits more closely into line with the teachings of the modern science of nutrition.

CHAPTER XXII

MEDICAL EVALUATION OF NUTRITIONAL STATUS

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Evaluation of nutritional status is designed primarily to determine whether a person is malnourished. At once this stated aim raises several questions. What is malnutrition? What are its specific manifestations? If it is to be recognized, its characteristics must be known. Which of these should be selected as a basis for detection? Assuredly the methods must be founded on qualities which adequately represent malnutrition.

The very name evaluation of nutritional status indicates that the procedure includes something more than placing a person in either of the two categories: well nourished or malnourished. If malnutrition is found it is also desirable to ascertain its severity. Malnutrition occurs in all degrees. If a sufficiently large number of persons at random were examined by the most sensitive and specific methods, their nutritional condition would form a continuous series from perfection to extreme malnutrition. It is necessary to classify the series into degrees, to establish standards and to have a scale of rating. Then a person's status may be compared with standards and rated accordingly. Here we are concerned with something more than detection of malnutrition; we also want to measure it. For this is needed a system of examination which is not only specific but also sensitive. The methods must permit distinction of fine differences in measuring malnutrition.

In answering the questions What is malnutrition? and What items should be examined? it will be seen that the concept of malnutrition, the methods and criteria of evaluating it are inseparably linked. For the methods and criteria reflect the views on the nature of malnutrition. All three aspects have been undergoing an evolution during the past half century.

CROSS SECTIONAL METHODS OF EXAMINATION

Most of the methods of examining for nutritional status have been devised for application on large groups of persons, especially school children and army recruits. Here the examination is a screening process that will both separate and rate the malnourished.

One of the early methods, the physician's estimate from inspection, has undergone a series of changes. In 1905 Koppe¹ regarded nutrition as one of eight components of constitution. To him nutritional status was indicated by the amount of panniculus adiposus. Each of the constitutional components, including subcutaneous fat, was rated in five grades. The grades for all components totaled and averaged gave the score for constitution. Obviously nutritional status was completely obscured in constitution.

In 1908 Gastpar² used three items for judging and five grades for designating nutritional status. Pupils were divided into two groups, anemic and nonanemic, according to the circulation in cutaneous and mucous membranes. The first group was then divided into two, the latter into three subgroups according to musculature and subcutaneous fat. The grades were: good, fair, poor, fair and anemia, poor and anemia.

Hogarth³ appraised nutrition as part of physical condition. The latter was composed of three factors: physical stature, general nutrition, circulation in the superficial membranes. Each factor could be rated in five possible grades. Musculature and panniculus adiposus were the basis of judgment for nutrition. The possible ratings were (1) excellent muscular development, (2) well nourished and healthy, (3) medium, (4) thin or fat and flabby tissues, (5) very thin. But nutrition lost much of its identity in the three figured score for physical condition.

According to Howarth⁴ physical state is evidenced by height, weight and nutrition. His basis of judging

1. Koppe, O.: *Wie bestimmen wir die Konstitution der Schüler*, *Ztschr. f. Schulgesundheitspf.* 18: Der Schularzt, 3: 219-224, 1905.

2. Gastpar: *Die Beurteilung des Ernährungszustandes der Schulkinder*, *Ztschr. f. Schulgesundheitspf.* 21: 689-702, 1908.

3. Hogarth, A. H.: *Medical Inspection of Schools*, London, Oxford University Press, 1909, chapter 11, pp. 158-159.

4. Howarth, W. J., in Kelynnack, T. N.: *Medical Examination of Schools and Scholars*, London, P. S. King & Son, 1910, chapter 3, p. 39.

nutrition was: skin and mucous membranes, hair, alertness, muscular tone. There were three grades of nutrition.

In the Dunfermline system⁵ the following points were taken into consideration: height and weight in relation to age; general appearance; mucous membranes, skin and subcutaneous tissues; muscular tone and development; facial expression, carriage, movements, voice, interest and attention. At first nutritional status was recorded as good (above average), medium (average) and bad (below average). Later "the nutrition of the healthy child of good social standing" was the basis of classification, being given the rating excellent. When nutritional status just fell short of this it was regarded as good. When it was on the borderline of serious impairment it was designated as "requiring supervision." When it was seriously impaired it received the notation "requiring medical treatment."

Against the systems of evaluation by inspection there was considerable criticism. In a frank critique the London County Council report⁶ for 1909 pointed out serious difficulties. Anemia was so complicated by complexion that it was difficult to assess by inspection. Furthermore, it stated, the physician himself introduced a large personal element.

Indeed, the shortcomings of the inspection methods were numerous and serious. At first nutrition was overshadowed as a component of constitution or physical condition. But, even when nutritional status was the specific and sole objective, clinical examination in practice showed lack of uniformity and agreement. The general criticism was that it failed because of subjectivity in judgment. There are reasons for much of this subjectivity. As has been noted, there was no agreement on items regarded as indicative of nutrition for judgment of status. Then too, standards were relative rather than absolute. Laveran⁷ remarked that estimate of status depended on comparison with variable or

5. Mackenzie, Alister: *Seventh Annual Report on the Medical Inspection of School Children in Dunfermline 1912-1913*, Edinburgh, Turnbull & Spears, pp. 18-20.

6. Report of the Education Committee of the London County Council Submitting the Report of the Medical Officer (Education) for the Twenty-One Months Ended 31st December, 1908, London, London County Council, 1909, pp. 16-19.

7. Laveran, quoted by Pignat: *Du coefficient de robusticité*, Bull. méd. 15: 373-376, 1901.

unsatisfactory standards. Conditions just previously or most frequently seen influenced the rating assigned to a person. Moreover, there was much variation in number and names of groups; i. e., in rating scale. But even when all these points of variation were fixed, there was still much disagreement. When a group of children were examined by several physicians, using the same items and scale, there was still no uniformity in the ratings.⁸ Derryberry⁹ stated "Whether a child is rated as malnourished or not depends more on the physician who is the examiner than it does on the actual condition of the child." It became clear that even under rigidly controlled conditions there was a large element of subjectivity in the physician's judgment.

In the need for an objective method of judging nutrition a new approach was taken. Since normal growth is a manifestation of satisfactory nutrition, growth was taken as a measure of the nutritive state. The immediate question then was: How shall growth be measured?

As weight and height had been used to follow growth and development, they were used to measure nutrition.¹⁰ They were referred to each other, and individually or in combination to age: weight for age, weight for height, weight for height and age, and height for age. Standard weights were derived from statistical analysis of data collected on children supposedly in good nutritive condition. These standards were presented in reference tables.¹¹ In other instances weight and height were used in a simple ratio to give an index number which could be compared with a standard.¹²

8. Franzen, Raymond: *Physical Measures of Growth and Nutrition*, New York, American Child Health Association, 1929, chapter 1, pp. 1-17. Derryberry.⁹

9. Derryberry, Mayhew: *Reliability of Medical Judgments on Malnutrition*, Pub. Health Rep. 53:263-268 (Feb. 18) 1938.

10. Oeder, Gustav: *Das Körpergewicht des erwachsenen Menschen bei normalen Ernährungszustand und seine Berechnung*, Ztschr. f. Versicherungsmed. 2:2-12 (Jan.) 1909. Paton, D. N., and Findlay, Leonard: *Child Life Investigations: Poverty, Nutrition and Growth; Studies of Child Life in Cities and Rural Districts of Scotland*, Medical Research Council, Special Report Series, No. 101, London, His Majesty's Stationery Office, 1926, pp. 48-57.

11. Baldwin, B. T., and Wood, T. D.: *Weight-Height-Age Tables for Boys and Girls*, New York, American Child Health Association, 1932.

12. Greenwood, Arthur: *The Health and Physique of School Children*, Westminster, P. S. King & Son, 1913, chapter 2, pp. 10-11.

As early as 1909 Oeder¹³ and Oppenheimer¹³ pointed to inaccuracies in using weight as the measure of nutrition. Gradually the reasons became clear. For one thing, as it was by no means certain what constituted normal growth, the suitability of available height and weight standards was open to question. Scarcely less difficult was the question: How much deviation from average should be allowed for individual variations? These points led to much cross criticism. But, troublesome as they were, there was still a more serious criticism.

From a study in which there was no more underweight in a group on a poor diet than in a group on a good diet,¹⁴ the validity of weight as an index of nutrition was considerably shaken. Indeed, selection by weight was much less accurate than by clinical examination¹⁵ when each was referred to dietary data. As might be expected, selection by weight and by clinical examination when compared directly showed serious disagreement.¹⁶ In this discrepancy the clinical examination, for all its acknowledged shortcomings, was regarded as superior. Unfortunate as were the instances when children were diagnosed as malnourished by weight but were well nourished according to clinical examination, much more serious were the instances when children rated by weight as well nourished showed pronounced signs of malnutrition. It was evident that

13. Oppenheimer, Karl: Ein Versuch zur objectiven Darstellung des Ernährungszustandes, *Deutsche med. Wchnschr.* **35**: 1835-1838, 1909.

14. Hughes, Elizabeth, and Roberts, Lydia: Children of Preschool Age in Gary, Indiana, Bureau Publication 122, U. S. Department of Labor, Children's Bureau, 1922, part II, pp. 101-102.

15. Roberts, Lydia: The Nutrition and Care of Children in a Mountain County of Kentucky, Bureau Publication 110, U. S. Department of Labor, Children's Bureau, 1922, pp. 28-32.

16. Manny, F. A.: A Comparison of Three Methods of Determining Defective Nutrition, *Arch. Pediat.* **35**: 88-94 (Jan.) 1918. Clark, Taliaferro; Sydenstricker, Edgar, and Collins, Selwyn D.: Weight and Height as an Index of Nutrition; Weight and Height Measurements of 9,973 Children Classified upon Medical Examination as "Excellent," "Good," "Fair" or "Poor" in Nutrition as Judged from Clinical Evidence, *Pub. Health Rep.* **38**: 39-58 (Jan. 12) 1923. Baker, S. Josephine, and Blumenthal, J. L.: Methods of Determining Malnutrition, *Nation's Health* **5**: 47-50 (Jan.) 1923. Clark, Taliaferro; Sydenstricker, Edgar, and Collins, Selwyn D.: The New Baldwin-Wood Weight-Height-Age Tables as an Index of Nutrition: The Application of the Baldwin-Wood Standard of Nutrition to 506 Native White Children without Physical Defects and with "Good" or "Excellent" Nutrition as Judged from Clinical Evidence, *Pub. Health Rep.* **39**: 518-525 (March 14) 1924. Dublin, L. I., and Gebhart, J. C.: Do Height and Weight Tables Identify Undernourished Children? New York, New York Association for Improving the Condition of the Poor, 1924.

methods employing weight as the measure were inaccurate for estimating the state of nutrition.

In retrospect it is seen that unwittingly the enormous misdirected labors over many years in using weight were based on a fallacy in logic. Because persons showing pronounced deviations in weight are malnourished, it was inferred erroneously that persons not showing these deviations are well nourished. Actually, on the basis of weight it is not possible to characterize normal nutrition. Nevertheless weight was extensively used in this country until 1930, when the mass of accumulated evidence against it overwhelmed it.

Meanwhile, as soon as the defects of methods using weight in association with height and age as a basis of judging nutrition became evident, steps designed to remedy them had been taken. Most attempts were aimed at supplying new standards in the hope of making the methods accurate. These modifications, developed simultaneously, took several lines.

One type was the determination of standards of weight in normal nutritive condition. In attempting to appraise the nutritive status of adults by weight, Oeder¹⁷ encountered difficulties similar to those in using the method during growth. He attempted to find the normal nutritive condition so that he might determine the range of body weight associated with it. Of bodily constituents, fat was found to be the one altered most extensively in starvation and adiposity, representing extremes of nutritive disturbance, and the one reacting most sensitively to change in nutrition. Consequently he regarded fatty tissue as the index of nutritive condition. He listed four signs of normal nutritive condition, including a definite thickness of fat layer on the abdomen. He recorded the normal range in the thickness of this fat layer and the corresponding body weight. Then his line of reasoning led him to displace use of weight by measurement of the fat layer on the abdomen.¹⁸

Another kind of attempt to improve the use of weight methods was the calculation of normal standards in relation to physique. By 1912 it was becoming apparent that variations in type of body build had to be

17. Oeder, Gustav: Der "normale" Ernährungszustand des erwachsenen Menschen, *Med. Klin.* 5 (2): 1225-1229, 1909.

18. Oeder, Gustav: Die Fettpolstendicke als Index des Ernährungszustandes bei Erwachsenen, *Med. Klin.* 5 (1): 657-662 (April 24) 1910.

considered in judging growth by weight and that these variations had to be taken into account in the prediction of normal weight. During the latter half of the nineteenth century several index numbers derived from formulas containing various bodily measurements had been used in following physical development or expressing body build or constitution.¹⁹ Some of these contained weight as a factor. As Bornhardt²⁰ pointed out, transposition in his equation made it possible to solve for weight. Several other formulas or ratios, most of them patterned after the earlier models, were proposed for determination of theoretical weight with which actual weight could be compared.²¹ In other instances the procedure was to measure body build by dimensions other than weight and to note the weight associated with them.²²

Still another approach ushered in the use of nutritional indexes. Recognizing the errors in judgment by weight and the subjectivity of a physician's inspection, Oppenheimer in 1909 devised a method that would be objective but have a clinical basis.²³ He argued that physicians, recognizing that certain bodily parts reflected malnutrition more sensitively and accurately than does

19. The early as well as the later indexes are cited in References on the Physical Growth and Development of the Normal Child, Publication 179, U. S. Department of Labor, Children's Bureau, 1927. They are described by Max Guttman (*Ist eine objective Beurteilung des Ernährungszustandes des Menschen möglich?*), *Arch. f. Kinderheilk.* 72:23-49, 1923; Paton, D. N., and Findlay, Leonard: *Child Life Investigations: Poverty, Nutrition and Growth; Studies of Child Life in Cities and Rural Districts of Scotland*, Medical Research Council, Special Report Series, No. 101, London, His Majesty's Stationery Office, 1926, pp. 48-57; and McCloy, C. H.: *Appraising Physical Status: The Selection of Measurements*, Iowa City, University of Iowa, 1936.

20. Bornhardt, A.: *Die Körperwägungen der Einberufenen als Mittel zur Bestimmung der Tauglichkeit zum Militärdienst*, St. Petersburg. med. Wehnschr. 3:108-109, 196-197, 1886.

21. Gaertner, Gustav: *Körpergewicht und Körperlänge des Menschen*, Wien. med. Wehnschr. 62:317-322 (Jan. 27) 1912. Oeder, Gustav: *Das Körpergewicht des erwachsenen Menschen bei normalem Ernährungszustand und seine Berechnung*; Ueber die Brauchbarkeit der "proportionellen" Körperlänge als Massstab für die Berechnung des Körpergewichts erwachsener Menschen bei normalem Ernährungszustand, *Med. Klin.* 5:461-465 (March 28) 1909; Die Gärtner'sche Normalgewichtstabelle für Erwachsene, *Berl. klin. Wehnschr.* 52:1086-1092 (Oct. 18) 1915; Ein neuer "Index ponderis" für den "zentral-normalen" Ernährungszustand Erwachsener, *Deutsche med. Wehnschr.* 42:1073-1074 (Aug. 31) 1916.

22. Pryor, Helen B., and Stolz, H. R.: *Determining Appropriate Weight for Body Build*, *J. Pediat.* 3:608-622 (Oct.) 1933. McCloy, C. H.: *Appraising Physical Status: The Selection of Measurements*, Iowa City, University of Iowa, 1936, chapter 4, pp. 43-65; *Appraising Physical Status: Methods and Norms*, Iowa City, University of Iowa, 1938, chapter 4, pp. 34-47.

23. Oppenheimer, Karl: Ueber eine Methode zur ziffermässigen Bestimmung des Ernährungszustandes, *Ztschr. f. Schulgesundheitspf.* 22:880-889, 1909; Ein Versuch zur objectiven Darstellung des Ernährungszustandes.²⁴

weight, based their judgment subconsciously on the relation of these parts. Each physician, he asserted, tended to rate the nutritional status according to his estimate of musculature and adipose tissue. But individual judgment of these parts differed appreciably because of the difficulty in making proper allowance for the complicated differences in body build. To overcome this difficulty, Oppenheimer selected three bodily dimensions which reflected the relation of body parts decisive in the physician's estimate and which could be objectively measured. From these three dimensions he propounded two formulas: one gave the measure of nutrition, which increased with age and growth; the other gave the quotient of nutrition, which was influenced only by nutritive condition. Twenty-five years later the same rationale²⁴ and almost the identical measurements were adopted in working out the ACH index,²⁵ except that a different relation of measurements and a reference table were used.

Attempts to make allowance for variations in body build in the appraisal of nutritional status took another direction. With the realization that the ratio of height-weight failed to indicate accurately whether the amount of muscle and fat corresponded to the skeleton, other sets of dimensions were suggested. From anthropometric studies of growth Pirquet²⁶ found that weight referred to sitting height in the form of a ratio yielded a numerical index, "pelidisi," which he regarded as an objective measure of nutritive condition.

At the same time the widespread prevalence of malnutrition in Austria and Germany during World War I created an emergency; the American War Relief Commission and Quakers²⁷ desired a rapid and objective method of selecting the children needing supplementary food. Ratios containing various physical measurements which had been used for many years to express body

24. Franzen, Raymond: *Physical Measures of Growth and Nutrition*, New York, American Child Health Association, 1929, chapter 1, pp. 1-17.

25. Franzen, Raymond, and Palmer, G. T.: *The ACH Index of Nutritional Status*, New York, American Child Health Association, 1934. *Nutritional Status Indices: Method of Obtaining Measures of Musculature, Subcutaneous Tissue and Weight with Allowance for Skeletal Build (Boys and Girls, 7 to 12 Years of Age)*, New York, American Child Health Association, 1935.

26. Pirquet, Clemens: *Sitzhöhe und Körpergewicht (System der Ernährung: II)*, *Ztschr. f. Kinderh.* 14: 211-228, 1916.

27. *Sonderheft über die Kinderspeisung in Deutschland*, Herausgegeben vom Deutschen Zentrallausschuss für die Auslandshilfe, E. V. Berlin, *Ztschr. f. Schulgesundheitspf.* 35: 177-240 (Nov. 7) 1922.

build, constitution or physical fitness were turned from their original purpose and were applied, either unchanged or changed, as measures of nutrition.¹⁹ Several new but similar ratios appeared, some containing weight as an item. In all of them a change in a measurement and therefore in the resulting quotient, the index number, was regarded as indicating a shift in the nutritive status. Since these equations contained measurements presumed to reflect body build, they were regarded as more sensitive and accurate than weight-height in evaluating nutritional status.

But evidence showed that all these indexes, formulas, equations and ratios aimed to refine or replace the height-weight method had its same defects.²⁴ They were vulnerable to the same criticisms. Actually, they revealed more about body build than about nutrition. Naturally the application of these methods to adults was based on other considerations than growth, but the results were just as unsuccessful as those on infants and children.

LONGITUDINAL PROCEDURE

In contrast to the preceding cross sectional methods of examining growth, the longitudinal procedure of following the growth curve was also suggested as a measure of nutrition. Greenwood²⁰ proposed that the percentage growth per year in height and weight, respectively, be the standard of comparison. Failure to increase in weight at a given rate would bring a designation of malnutrition. According to one criterion, lack of gain or loss in weight for each month of three successive months was cited as a means of screening

28. Clark, Taliaferro; Sydenstricker, Edgar, and Collins, Selwyn D.: Indices of Nutrition: Application of Certain Standards of Nutrition to 506 Native White Children without Physical Defects and with "Good" or "Excellent" Nutrition as Judged from Clinical Evidence, *Pub. Health Rep.* **38**: 1239-1270 (June 8) 1923. Guttman, Max: Ist eine objektive Beurteilung des Ernährungszustandes des Menschen möglich? *Arch. f. Kinderh.* **72**: 23-49, 1923. Paton, D. N., and Findlay, Leonard: Child Life Investigations: Poverty, Nutrition and Growth; Studies of Child Life in Cities and Rural Districts of Scotland, Medical Research Council, Special Report Series, No. 101, London, His Majesty's Stationery Office, 1926, pp. 57-65. Souther, Susan P.; Eliot, Martha M., and Jeness, Rachel M.: A Comparison of Indices Used in Judging the Physical Fitness of School Children, *Am. J. Pub. Health* **29**: 434-438 (May) 1939. Jeness, Rachel M., and Souther, Susan P.: Methods of Assessing the Physical Fitness of Children, Bureau Publication 263, U. S. Department of Labor, Children's Bureau, 1940.

29. Greenwood, Arthur: The Health and Physique of School Children, Westminster, P. S. King & Son, 1913, chapter 2, p. 11.

children with poor growth.³⁰ It has been asserted that the weight curve is the most accurate measure of growth.³¹ This method has been successfully used in animal experiments in nutrition. But the animals were inbred and selected. Besides, they were subjected to dietary deficiencies with pronounced interference with growth. For both human beings and experimental animals, the so-called normal growth curves have changed over the past three decades. No one knows whether greatest growth has yet been obtained; whether greatest is optimum; in short, what optimum growth is. And no one knows how slight a deviation in growth curve should be regarded as malnutrition. Thus the very same objections to use of absolute weight may be leveled against the use of the growth curve.

Recently there appeared a method which combines the longitudinal and cross sectional procedures permitting application of either.³² A grid prepared from height, weight and age is purported to give ratings during the period of growth on physique, development, nutrition and physical status. The slope or gradient of the developmental curve is said to give a measure of nutritional status. If measurements are limited to a single observation, a tentative estimate of nutrition can be made. Since height, weight and age are the only measurements used, it is similar to previous growth methods and it may therefore be open to the same difficulties and objections. Its class limits, admittedly arbitrary, are different, but it remains to be seen whether they are free of the defects which have restricted the use of all growth methods.

There is no desire to disparage or discredit the proper use of deviations in growth, shown by height or weight, as an indication of malnutrition. It should never be forgotten that an obvious and unequivocal disturbance in weight—or other measurements—indicate serious malnutrition. About this there has never been an argument. Used within this limitation—and this a serious limitation—a weight method has distinct value.

30. Turner, C. E., and Nordstrom, Alfred: Extent and Seasonal Variations of Intermittency in Growth, *Am. J. Pub. Health* 28: 499-505 (April) 1938.

31. Friedenthal, Hans: *Allgemeine und spezielle Physiologie des Menschenwachstums*, Berlin, Julius Springer, 1914, p. 47.

32. Wetzel, N. C.: Physical Fitness in Terms of Physique, Development and Basal Metabolism with a Guide to Individual Progress from Infancy to Maturity: A New Method for Evaluation, *J. A. M. A.* 116: 1187-1195 (March 22) 1941.

It is when it is used beyond its restrictions that its fundamental defects emerge. It breaks down at the very point at which it is most needed, the borderline zone. It does not satisfactorily separate the slightly abnormal from the normal. Then when the scale is set at unequivocal limits the method is not a sufficiently sensitive screen for detecting malnutrition. In addition, for other reasons it will be seen that it is too inadequate and insensitive to serve as the primary screen of malnutrition.

In 1935 Dr. Roberts³³ wrote "It should be understood at the outset that the whole question of the use of growth criteria for assessing nutrition has been undergoing severe criticism in the last few years, and most of the commonly used methods have been largely discredited. We are indeed at the moment in a situation where we have lost confidence in the old methods and as yet have nothing new that is satisfactory to take their place." When this was written, little was at hand. But developments were in the offing. Through new knowledge nutrition had already extended into a new and vast domain. Among its many practical aspects, it opened a new and different approach to the evaluation of nutritional status. In the last few years, progress in this direction has brought forth new methodologies and has accentuated the distinct and fundamental limitations of previous procedures based on growth.

DEFICIENCY DISEASES

Following Eijkman's experimental production of beriberi by diet in 1897, Grijns formulated the conception of deficiency diseases.³⁴ He showed that certain foods contained an unknown essential substance which cured or protected against beriberi. When foods lacking the essential were eaten, beriberi resulted. It was clear that deficiency of an essential substance in food produced disease. To this substance Funk gave the name "vitamine."

It had long been known that calories were necessary for growth and maintenance; for with insufficient caloric intake, impaired growth or actual loss of weight, i. e.

33. Roberts, Lydia J.: *Nutrition Work with Children*, revised edition, Chicago, University of Chicago Press, 1935, chapter 3, pp. 42-43.

34. The developments leading to the modern concept of dietary essentials are reviewed in the book by E. V. McCollum, Elsa Orent-Keiles and H. G. Day: *The Newer Knowledge of Nutrition*, ed. 5, New York, Macmillan Company, 1939, chapter 2, pp. 15-31.

undernutrition, ensued. During the decade 1912-1922 it was found that a series of chemically unidentified substances, present in very small amounts in natural foods, were likewise essential for growth and maintenance. When the diet was deficient in any one of them, retarded growth or actual decrease in weight took place.

In the same period it was further shown that the "vitamine" protecting against beriberi was identical with one of the unidentified substances indispensable for growth. Then from animal experiments it was found that lack of each of the growth substances resulted in a separate, specific disease which had its analogue in man. Thus scurvy, xerophthalmia and rickets were found to be deficiency diseases, each arising from lack of a different substance. In this dual role each substance was essential not only for prevention of these diseases but also for promotion of growth. As additional essential substances were demonstrated, it was noted that a deficiency in each not only impaired growth but also produced a specific disease. More recently, pellagra and ariboflavinosis have been identified as deficiency diseases. Thus it has been demonstrated that lack of each essential substance produces a specific deficiency disease.

According to accepted nomenclature, each substance came to be designated by the generic name vitamin and an alphabetic letter. Thus xerophthalmia, beriberi, keratitis, pellagra, scurvy and rickets, the major deficiency diseases which historically have occurred in epidemics and endemics, resulted from lack of vitamins A, B₁, B₂, P-P, C and D respectively. With the chemical isolation and identification of the vitamins, it has been convenient to give each a more descriptive name as follows: B₁, thiamine; B₂, riboflavin; P-P, niacin (nicotinic acid); C, ascorbic acid. Vitamins A and D have yet to be given such a designation.

Meanwhile the concept of deficiency diseases had been extended to embrace those disorders arising from deficiency of essentials other than vitamins, e. g. protein, calcium and iron. Thus, lack of an essential, whether a vitamin, protein or mineral, produces its own particular and specific deficiency disease.

From these facts may be formulated the principles epitomizing the newer knowledge of diet and nutrition: (1) a number of essential substances are contained in

food; (2) a deficiency of each essential substance in the diet interferes with growth and maintenance and induces a disease; (3) the relationship between the nature of the dietary deficiency and of the resulting disease is characterized by specificity. These principles have had a profound influence on nutritional science, especially the concept of nutritional status and means of appraising it.

This knowledge of dietary essentials gave a new approach to the detection of malnutrition. It suggested surveys in which diets were analyzed for deficiencies in the essential items.³⁵ This procedure is based on the assumption that evidence of dietary deficiency indicates impaired nutritional status, usually in the form of deficiency diseases. Despite its many possible sources of unavoidable inaccuracies, the dietary method yields highly informative results. But it has several drawbacks. It is costly, laborious and time consuming. By the time the data are collected and analyzed, the information is obtained many months after it is needed. Then too, it reveals only the most recent dietary habits. Thirdly, its evidence on malnutrition is indirect. Fourthly, it indicates only the malnutrition due to dietary deficiency. Nevertheless the information derived from it has been helpful, since deficient diet is the most frequent cause of malnutrition. To furnish information on cause is really its principal use. This method has shown that there is nationwide consumption of deficient diets³⁶ and suggests that there is widespread prevalence of malnutrition.

Along with the recognition that dietary deficiencies produce specific diseases came a period of closer study of these diseases leading gradually over the years to improvement in their detection. At first before their etiology was known these diseases, since they mostly occurred in combination in the same person, were not clearly differentiated and were therefore frequently confused. In time the major deficiency diseases were separated by their main characteristics and several accompanying signs. Even today this work of resolving deficiency diseases into pure form continues.

35. Bigwood, E. J.: *Guiding Principles for Studies on the Nutrition of Populations*, Geneva, League of Nations, Health Organization, Technical Commission on Nutrition, 1939, part I, pp. 20-137.

36. Stiebeling, Hazel K., and Phipard, Esther F.: *Diets of Families of Employed Wage Earners and Clerical Workers in Cities*, Circular 507, U. S. Department of Agriculture, Bureau of Home Economics, 1939.

Through inducing the experimental form and through curing the natural form by pure specific therapy, it has been possible to elucidate much about the specific and characteristic signs, the sequence of events and the site of early lesions in each major deficiency disease. In all this, animal experimentation has given many valuable clues. As a result, our knowledge of each deficiency disease in its acute manifest form has been greatly extended and refined. Not a few treatises have been written on these diseases. The older books contain very complete descriptions, although many points must be interpreted in the light of latter day advances.³⁷ Recent books and articles present newer developments.³⁸

37. Avitaminosen und verwandte Krankheitszustände, edited by W. Stepp and P. György, spezieller Teil in Enzyklopaedie der klinischen Medizin, Berlin, Julius Springer, 1927. Vedder, E. B.: Beriberi, New York, William Wood & Co., 1913. Marie, A.: Pellagra, translated by C. H. Lavinder and J. W. Babcock, Columbia, S. C., State Company, 1910. Wood, E. J.: A Treatise on Pellagra for the General Practitioner, New York, D. Appleton & Co., 1912. Niles, G. M.: Pellagra, an American Problem, Philadelphia, W. B. Saunders Company, 1912. Roberts, S. R.: Pellagra: History, Distribution, Diagnosis, Prognosis, Treatment, Etiology, St. Louis, C. V. Mosby Company, 1914. Harris, H. F.: Pellagra, New York, Macmillan Company, 1919. Hess, A. F.: Scurvy Past and Present, Philadelphia, J. B. Lippincott Company, 1920. Hess, A. F.: Rickets Including Osteomalacia and Tetany, Philadelphia, Lea & Febiger, 1929.

38. The Vitamins: A Symposium Arranged Under the Auspices of the Council on Pharmacy and Chemistry and the Council on Foods of the American Medical Association, Chicago, American Medical Association, 1939. Youmans, J. B.: Nutritional Deficiencies, Philadelphia, J. B. Lippincott Company, 1941. Williams, R. R., and Spies, T. D.: Vitamin B₁ (Thiamine) and Its Use in Medicine, New York, Macmillan Company, 1938. Jolliffe, Norman: Vitamin Deficiencies and Liver Cirrhosis in Alcoholism, Quart. J. Stud. Alcohol 1: 517-557 (Dec.) 1940. The Neuropsychiatric Manifestations of Vitamin Deficiencies, J. Mount Sinai Hosp. 8: 658-667 (Jan.-Feb.) 1942. Weiss, Soma, and Wilkins, R. W.: The Nature of the Cardiovascular Disturbances in Nutritional Deficiency States (Beriberi), Ann. Int. Med. 11: 104-148 (July) 1937; The Nature of the Cardiovascular Disturbances in Vitamin Deficiency States, Tr. A. Am. Physicians 51: 341-371, 1936. Sebrell, W. H., and Butler, R. E.: Riboflavin Deficiency in Man: A Preliminary Note, Pub. Health Rep. 53: 2282-2284 (Dec. 30) 1938. Kruse, H. D.; Sydenstricker, V. P.; Sebrell, W. H., and Cleckley, H. M.: Ocular Manifestations of Aribioflavinosis, Pub. Health Rep. 55: 157-169 (Jan. 26) 1940. Sydenstricker, V. P.; Sebrell, W. H.; Cleckley, H. M., and Kruse, H. D.: The Ocular Manifestations of Aribioflavinosis, J. A. M. A. 114: 2437-2445 (June 22) 1940. Harris, Seale: Clinical Pellagra, St. Louis, C. V. Mosby Company, 1941. Sydenstricker, V. P., and Armstrong, E. S.: A Review of Four Hundred and Forty Cases of Pellagra, Arch. Int. Med. 59: 883-891 (May) 1937. Spies, T. D.: Pellagra, in A Textbook of Medicine by American Authors, ed. 5, edited by R. L. Cecil, Philadelphia, W. B. Saunders Company, 1940, pp. 624-631. Elliot, Martha M., and Park, E. A.: Rickets, in Brennemann's Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1938, vol. I, chapter 36. Mackay, H. M. M., and Goodfellow, L.: Nutritional Anemia in Infancy with Special Reference to Iron Deficiency, Medical Research Council, Special Report Series, No. 157, London, His Majesty's Stationery Office, 1931. Youmans, J. B.: The Diagnosis of Nutritional Edema with Particular Reference to the Determination of Plasma Proteins and Consideration of their Behavior; in Nutrition: The Newer Diagnostic Methods, Proceedings of the Round Table on Nutrition and Public Health, New York, Milbank Memorial Fund, 1938, pp. 166-173.

But with all this knowledge the occurrence of deficiency diseases in this country has not been generally noted except in city hospitals or endemic regions. Although nationwide dietary inadequacies have been revealed by surveys, frank deficiency diseases on such a scale have not been seen. According to their concept, clinicians rightly assert that they do not see deficiency diseases. But they are incorrect in concluding that there is no widespread prevalence of them. What are the reasons for this apparently irreconcilable conflict between the evidence from dietary surveys and from clinical observations? It is probable that many classic cases pass unrecognized. But even if these were detected and included, the statistics on the prevalence of deficiency disease would not come near approaching the figures on faulty diets recorded in surveys. There is a more significant reason for the seeming discrepancy. In assertions by clinicians that deficiency diseases are not generally prevalent, the traditional severe acute form has been meant. In this country this classic form is relatively infrequent; instead, the deficiency diseases are present in other forms.

The predominant clinical point of view has carried the concept that a deficiency disease begins or has its significance when it becomes perceptible, usually on simple inspection. Often all or most signs must be present. Clearly that point is not the beginning of the disease. Rather, the disorder is already well advanced before it is diagnosed. Such a practice does not detect the disease in its early or mild form. Over the years, numerous physicians have recognized this point.

Several early investigators attempted to divide the course of scurvy and pellagra into stages; they noted the earliest stage and its characteristics. Some, like Roussel,³⁹ interested in early diagnosis, set down their observations on the earliest sign, stressing the importance of discovering the site of initial change. Moreover, they distinguished a period before the disease proper appeared, before its well known signs were fully developed. As early as 1541 Echthius⁴⁰ enumerated symptoms by which "an approaching scurvy

39. Roussel, Théophile: *Traité de la pellagre et des pseudo-pellagres*, Paris, J. B. Baillière et fils, 1866, chapter 1, pp. 4, 10.

40. Echthius, Jo.: *De scorbuto, vel scorbutica passione*, Epitome, 1541; cited by Lind, James: *A Treatise on the Scurvy*, ed. 3, London, S. Crowder, 1772, part 3, chapter 2, pp. 302-305.

might be foretold"; in 1567 Wierus⁴¹ described similar observations. Many subsequent observers recognized a prodromal, incipient or latent period in both pellagra⁴² and scurvy.⁴³ Added still later were the names *forme fruste*, *prepellagra* or *prescurvy*, subclinical state. About 1917 other investigators conceived that a deficiency disease like scurvy might exist below the level of clinical detection by any sign, but to this state they applied names already carrying other connotations. Thus several names were applied to the same state; conversely, several states were designated by the same name or names. In scurvy Hess⁴⁴ drew distinctions which

41. Wierus, Jo.: *Medicarum observationum hactenus incognitarum* lib. I. de scorbuto cited by Lind, James: *A Treatise on the Scurvy*, ed. 3, London, S. Crowder, 1772, part 3, chapter 2, pp. 308-311.

42. Frapolli, Francisci: *Annadversiones in Morbum, Vulgo Pellagram*, Milan, Joseph Galeatium, 1771, pp. 19-21. Jansen, W. X.: *De Pellagra, Morbo in Mediolanensi Ducatu Endemio Lugundi Batavorum*, 1787, in Frank, J. P.: *Delectus Opusculorum Medicorum Antehac in Germaniae Diversis Academicis Editorum*, Ticini, P. Galeatii, 1790, 9, pp. 325-387. Titius, S. C.: *Oratio de Pellagrae Morbi inter Insulariae Austriacae Agricolae Grassantis Pathologia Viteburg*, 1792, in Frank, J. P.: *Delectus Opusculorum Medicorum Antehac in Germaniae Diversis Academicis Editorum*, Ticini, P. Galeatii, 1793, 12, pp. 121-176. Lussana, Filippo: *Sulla Pellagra*, *Ann. Univ. de Med.* **169**: 449-520, 1859. Tuczek, Franz: *Klinische und anatomische Studien über die Pellagra*, Berlin, Fischer's Medic. Buchhandlung, 1893, pp. 10-25. Babes, Victor, and Sion, V.: *De Pellagra*, in *Specielle Pathologie und Therapie*, edited by Hermann Nothnagel, Vienna, Alfred Hölder, 1901., vol. 24, part 2, 2d half section 3, pp. 39-52. Roussel: *Traité de la pellagre et pseudo-pellagres*.⁴⁰ Sandwith, F. M.: *Pellagra in Egypt*, *J. Trop. Med.* **1**: 63-70 (Oct.) 1898; *Pellagra*, *Encyclopaedia Medica*, Edinburgh, William Green & Sons, 1901, vol. 9, pp. 244-249.

43. Lind, James: *A Treatise on the Scurvy*, ed. 3, London, S. Crowder, 1772, part 2, chapter 2, pp. 98-117. Echthius.⁴⁰ Wierus.⁴¹ Brunerus, Balthazaro: *De scorbuto tractatus duo*, 1589, cited by Lind, James: *A Treatise on the Scurvy*, ed. 3, London, S. Crowder, 1772, part 3, chapter 2, pp. 315-317. Curran, J. O.: *Observations on Scurvy as It Has Lately Appeared Throughout Ireland, and in Several Parts of Great Britain*, *Dublin Quart. J. M. Sc.* **4**: 83-134 (Aug and Nov.) 1847. Immerman, H.: *Scorbut. Scharbock* (Engl.: Scurvy), in *Handbuch der allgemeinen Ernährungsstörungen*, by Birch-Hirschfeld, H. Senator and I. Immerman, 2d half, pp. 581-603, in *Handbuch der speciellen Pathologie und Therapie*, edited by H. V. Z. Ziemssen. Leipzig, F. C. W. Vogel, 1876, vol. 13, 2d. half. Höjer: *Studies in Scurvy*.⁴⁷ Hutinel, V.: *Les maladies des enfants*, Paris, Asselin and Houzeau, 1909 vol. 2, pp. 451-453. Czerny, A. D.: *Die Ernährung der deutschen Kinder während des Weltkrieges*, *Monatschr. f. Kinderh.* **21**: 1-13 (April) 1921. Hess: *Subacute and Latent Infantile Scurvy*.⁴⁴ Morawitz, P.: *Ueber hamorrhagische Diathesen*, in *Jahreskurse für ärztliche Fortbildung*, Munich, J. F. Lehmanns, 1919, vol. 10, pp. 9-49. Mouriquand, G., and Michel, P.: *Les états scorbutiques passagers et récidivants*, *Compt. rend. Soc. de biol.* **1**: 734-737, 1921. Godlewski, Henri: *Carence partielle et préscurbut*, *Presse méd.* **29**: 682-683 (Aug. 27) 1921. Nassau, Erich, and Singer, M. J.: *Zur Kenntnis des Vorstadiums der Barlow'schen Krankheit*, *Jahrb. f. Kinderh.* **98**: 44-62, 1922. Leichtentritt: *Klinische und experimentelle Barlow-Studien*.⁴⁵ Kleinschmidt, H.: *Latenter Skorbut oder infektiöse Purpura?* *Arch. f. path. Anat. u. Physiol.* **246**: 131-139, 1923. Freund: *Barlow'sche Krankheit*.⁴⁶ Frölich, Theodor: *Malnutrition and Latent Scurvy*, *Arch. Dis. Childhood* **10**: 309-312, 1935.

44. Hess, Alfred F.: *Subacute and Latent Infantile Scurvy: The Cardiorespiratory Syndrome (a New Sign)*, *J. A. M. A.* **68**: 235-239 (Jan. 27) 1917.

defined these several concepts. He recognized three types of scurvy: the florid, with well developed signs of the full blown condition; the subacute, the commoner form, presenting a group of incompletely developed symptoms; the latent, resulting from a negative balance in vitamin C during the period prior to the onset of clinical manifestations. In view of the importance previously attached to weight as an index of nutritional status, it is significant that Hess emphasized the normal weight of children affected with subacute scurvy.

At the same time it was recognized that scurvy might be observed in still another state, the so-called monosymptomatic state.⁴⁵ Cheadle⁴⁶ in 1878 had forecast this eventuality. This occurrence has been confirmed not only for scurvy but also for pellagra. During the last decade numerous epidemics or instances of gingivitis⁴⁷ and glossitis⁴⁸ demonstrated to be attributable to deficiency in ascorbic acid and niacin respectively have been observed. Some investigators have distinguished degrees of one sign in avitaminosis C.⁴⁹

45. Leichtenritt, Bruno: *Klinische und experimentelle Barlow-Studien*, Ztschr. f. d. ges. exper. Med. **29**: 658-708, 1922. Freund, Walther: *Barlow'sche Krankheit: Kindlicher Skorbut*, in *Handbuch der Kinderheilkunde*, edited by M. von Pfaundler and A. Schlossman, ed. 3, Leipzig, F. C. W. Vogel, 1923, vol. 1, pp. 716-717.

46. Cheadle, W. B.: Three Cases of Scurvy Supervening on Rickets in Young Children, *Lancet* **2**: 685-687 (Nov. 16) 1878.

47. Hanke: Diet and Dental Health.⁴⁹ Kramer: Untersuchungen über C-Hypovitaminosen bei Parodontopathien nach der Methode Tillman, modifiziert von Jezler und Niederberger, der deutsche Militärarzt **2**: 489-493 (Dec.) 1937. Demoulin, Pierre: Résultats favorables obtenus par l'emploi de la vitamine C dans la thérapeutique des gingivites marginales, *Rev. belge de stomat.* **35**: 164-170 (June) 1938. Roff, F. Stanley, and Glazebrook, A. J.: The Therapeutic Application of Vitamin C in Periodontal Disease, *J. Roy. Nav. M. Serv.* **25**: 340-348 (Oct.) 1939; The Therapeutic Use of Vitamin C in Gingivitis of Adolescents, *Brit. Dent. J.* **68**: 135-141, 1940. Bouillat and Ramian-drasso, A.: Dix-huit gangrènes de la bouche dont treize guéries, traitées par l'acide ascorbique, *Presse méd.*, 1st sem. 541 (May 22-23) 1940. Campbell, H. Gordon, and Cook, R. P.: Treatment of Gingivitis with Ascorbic Acid, *Brit. M. J.* **1**: 360-361 (March 8) 1941. Dechaume, M.: Gingivo-arthritides dentaires et avitaminoses, *J. Canad. Dent. A.* **7**: 420-422 (Aug.), 471-474 (Sept.) 1941. Martí, Gusto Solsona, and Sales, Ricardo I.: Vitamina C: Vitaminoterapia en odontología, *Rev. Odont.* **29**: 73-80 (Feb.) 1941. Crane and Woods.⁴⁹

48. Jamin, H.: Stomatit d'autone, *Arch. Inst. Pasteur de Tunis* **14**: 126-129 (No. 1) 1925. Nogue: Epidémie de glossite observée au Sénégal, *Bull. d. Soc. path. exot. et de sa fil. de l'Ouest-Africain* **18**: 501-507 (No. 6) 1925. Mathis, C., and Guillet: Sur la nature de l'épidémie de glossites observée au Sénégal, *ibid.* **18**: 586-590 (No. 7) 1925. Katzenellenbogen, I.: Ueber eine epidemische Glossitis in Palästina, *Arch. f. Dermat. u. Syph.* **154**: 269-277, 1928. Aykroyd, W. R.; Krishnan, B. G., and Passmore, R.: Stomatitis of Dietary Origin, *Lancet* **2**: 825-828 (Oct. 14) 1939. Katzenellenbogen, I.: Nicotinic Acid in Endemic Glossitis, *Lancet* **1**: 1260-1262 (June 3) 1939.

49. Hanke, Milton T.: *Diet and Dental Health*, Chicago, University of Chicago Press, 1933. Crane, Marian M., and Woods, Philip W.: A Study of Vitamin C Nutrition in a Group of School Children, *New England J. Med.* **224**: 503-509 (March 20) 1941.

Despite the differences in concepts about the several states and the lax use of terms applied to them, all investigators have agreed that most deficiency diseases occur in these states.

EARLY DIAGNOSIS

In recent years there has been a distinct trend toward early diagnosis of all diseases. It has been recognized that a disease starting with internal manifestations cannot be seen and may yield no signs until it is far advanced, even more so if the lesion is in a silent area, that a disease with early external signs may pass unnoticed into an internal phase or that disease with a persistent or progressive external lesion may develop to a considerable point below the level of perception. In short, most disease has reached the advanced state before it is detected by the unaided senses; its early or mild stage develops unobserved.

The trend to diagnosis of early or mild disease showed the limitations of the unaided senses. It became necessary to turn to instruments or procedures that would reveal changes within the body or extend vision beyond the limits of the unaided eye. The x-rays, the Wassermann reaction, chemical methods for blood, urine and tissue and the microscope for examination of blood, urine and tissue have added greatly to the physician's skill in earlier detection and diagnosis. Similarly, long ago the pathologist, recognizing that much was occurring below the threshold of his vision, turned to the microscope to open the realm of cellular pathology.

So it has been with the detection of deficiency diseases. The early and mild states are below the manifest level. The pathogenesis of deficiency diseases makes the existence of these states thoroughly understandable. Among the manifestations of a deficiency disease on a dietary basis are lowered concentrations of the essential factor in the blood, depleted storage in the body's reservoirs, diminished excretion, microscopic change in the tissue in the initial site, gross morphologic and functional change. These manifestations, it should be stated, are not necessarily or ordinarily concurrent. To detect these states below the manifest level, investigators have had recourse to new procedures and instruments. For most deficiency diseases these states have been demonstrated by appropriate methodology. Hess's "

visualization of a state characterized by a negative balance in the vitamin has been confirmed by biochemical methods in analyses of blood and urine. Indeed, low blood values for ascorbic acid have been found in a definite proportion of population samples.⁵⁰ True, some investigators have argued that such values for ascorbic acid in the absence of other signs do not constitute scurvy. Judged by clinical criteria, the condition is not scurvy. Not until it has advanced to macroscopic tissue changes and developed signs is it designated scurvy. But that view draws a purely arbitrary distinction. Its justification is that it differentiates two states of severity in the process. One is the lesser developed state, the other the fully developed disease. But whatever the former is called, it is a step in the process. As a practical matter it may call for treatment.

Several procedures have been employed to elicit or detect the so-called monosymptomatic state before the sign has become manifest. It is obvious that the value of this approach for recognition of the incipient deficiency disease depends on testing or examining for the earliest sign. Instruments and methods have been devised for the detection of night blindness⁵¹ and capillary fragility,⁵² as evidence of avitaminoses A and C respectively. These conditions occur, but they are not monosymptomatic; for it has been shown that they are not the earliest signs of these avitaminoses.⁵³

50. Kruse, H. D.: Chemical Methods for Determining the Plasma Level of Vitamin C. *Am. J. Pub. Health* **31**:1079-1082 (Oct.) 1941. Milam, D. F.: A Nutrition Survey of a Small North Carolina Community, *ibid.* **32**:406-412 (April) 1942. Milam, D. F., and Wilkins, Walter: Plasma Vitamin C Levels in a Group of Children Before and After Dietetic Adjustment, *Am. J. Trop. Med.* **21**:487-491 (May) 1941.

51. Jeans, P. C., and Zentmire, Zelma: A Clinical Method for Determining Moderate Degrees of Vitamin A Deficiency, *J. A. M. A.* **102**:892-895 (March 24) 1934. Hecht, Selig: Dark Adaptation and the Diagnosis of Avitaminosis A. *Nutrition: The Newer Diagnostic Methods*, New York, Proceedings of the Round Table on Nutrition and Public Health, Sixteenth Annual Conference of the Milbank Memorial Fund (March 29-31) 1938, pp. 32-62.

52. Hess, A. F., and Fish, Mildred: Infantile Scurvy: The Blood, the Blood Vessels and the Diet, *Am. J. Dis. Child.* **8**:385-405 (Dec.) 1914. Göthlin, G. F.: A Method of Establishing the Vitamin C Standard and Requirement of Physically Healthy Individuals by Testing the Strength of Their Capillaries, *Skandinav. Arch. f. Physiol* **61**:225-270 (May) 1931.

53. Hunt, Eleanor P., and Hayden, Kenneth M.: Medical Evaluation of Nutritional Status: IX. The Reliability of Visual Threshold During Dark Adaptation as a Measure of Vitamin A Deficiency in a Population Group of Low Income, *Milbank Memorial Fund Quart.* **20**:139-168 (April) 1942. Kruse, H. D.: The Gingival Manifestations of Avitaminosis C, with Especial Consideration of the Detection of Early Changes by Biomicroscopy, *ibid.* **20**:290-323 (July) 1942.

More illuminating on the existence of the early state in a deficiency disease has been the observation of morphologic changes imperceptible to the unaided eye. Beginning changes in bones in infantile scurvy revealed by x-ray examination have been described.⁵⁴ Biomicroscopy, however, has disclosed still more about the early state of several deficiency diseases. Just as the microscope was highly useful to the pathologist in extending his range of vision to lesser changes in post-mortem tissue, it has now proved highly informative to apply it in deficiency diseases to changes in living tissues. It is particularly revealing when the tissue site among the first showing changes is selected for observation. Using this procedure, I have found early specific biomicroscopic changes in four deficiency diseases: in the conjunctiva in avitaminosis A,⁵⁵ in the cornea in ariboflavinosis,⁵⁶ in the tongue in aniacinosis⁵⁷ and in the gum in avitaminosis C.⁵⁸

Thus, alteration in transport and storage and microscopic changes in tissue show that deficiency diseases do exist in an early state which is undetectable by ordinary clinical methods.

In this morphologic study of these deficiency diseases, with biomicroscopic in conjunction with macroscopic examination, it was possible to see all gradations and to reconstruct the sequence of changes. These observations, combined with the results from administration of specific therapy, revealed new states. Besides the severe and early acute forms, I noted chronic states of varying intensity from mild to severe. These chronic states took on immediate significance because of their predominance in the population.

54. Park, E. A.; Guild, Harriet G.; Jackson, Deborah, and Bond, Marian: The Recognition of Scurvy with Especial Reference to the Early X-Ray Changes, *Arch. Dis. Childhood* **10**: 265-294 (Aug.) 1935.

55. Kruse, H. D.: Medical Evaluation of Nutritional Status: IV. The Ocular Manifestations of Avitaminosis A, with Especial Consideration of the Detection of Early Changes by Biomicroscopy, *Pub. Health Rep.* **56**: 1301-1324 (June 27) 1941; *Milbank Memorial Fund Quart.* **19**: 207-240 (July) 1941.

56. Kruse, H. D.; Sydenstricker, V. P.; Sebrell, W. H., and Cleckley, H. M.: Ocular Manifestations of Ariboflavinosis, *Pub. Health Rep.* **55**: 157-169 (Jan. 26) 1940. Sydenstricker, V. P.; Sebrell, W. H.; Cleckley, H. M., and Kruse, H. D.: The Ocular Manifestations of Ariboflavinosis, *J. A. M. A.* **114**: 2437-2445 (June 22) 1940.

57. Kruse, H. D.: The Lingual Manifestations of Aniacinosis, with Especial Consideration of the Detection of Early Changes by Biomicroscopy, *Milbank Memorial Fund Quart.* **20**: 262-289 (July) 1942.

58. Kruse, H. D.: The Gingival Manifestations of Avitaminosis C, with Especial Consideration of the Detection of Early Changes by Biomicroscopy, *Milbank Memorial Fund Quart.* **20**: 290-323 (July) 1942.

While each of the four deficiency diseases avitaminosis A, ariboflavinosis, aniacinosis and avitaminosis C has its individuality as a separate and specific entity, all in the evolution and recession of their particular lesions showed a similarity in their biologic behavior. They reflected a definite biologic pattern. From this was elaborated a concept of deficiency states, their nature, their evolution, how they may be recognized and their response to specific therapy.⁵⁹

According to this concept, the specific pathologic process in a tissue in a deficiency disease⁶⁰ is characterized by velocity, intensity and duration. Of the velocities occurring, the range may be classified arbitrarily and most simply into two principal categories which are subdivided. The acute process is rapid in appearing, in running its course and in receding under treatment. Somewhat less rapid is the subacute or mild acute process. Differing from these in velocity, the chronic process is slow in onset, progress and response to treatment. Even slower is the mild chronic process.

Since the pathologic process may be of any intensity, it is convenient to graduate arbitrarily the range in two degrees, mild and severe. Therefore the acute and the chronic process may be either mild or severe. With grouping by form and intensity, the simplest classification of processes provides the categories mild acute, mild chronic, severe acute and severe chronic. These are the same groups that were enumerated in designating a process according to its velocity.

If uninterrupted, the process manifests its changes in a definite sequence which may be divided into stages. Therefore in each of the categories it may be divided into stages. Naturally the duration of the process will be a factor determining its stage.

STATES OF AVITAMINOSIS

From the concept of deficiency states it may be seen that an avitaminosis includes all forms, degrees and

59. Kruse, H. D.: A Concept of Deficiency States, *Milbank Memorial Fund Quart.* 20: 245-261 (July) 1942.

60. To many persons the term "deficiency disease" connotes a disorder arising solely from a deficiency in the diet. True, dietary inadequacy is the most common cause; but there are many other causes and conditioning factors. They are discussed in a separate article in this series by Dr. Norman Jolliffe. As the result of any of these causes and conditions, tissues are deficient in or cannot use the essential. It is desirable that the term deficiency carry this broader meaning.

stages. Under this classification the classic deficiency disease, as originally described, represents the severe acute state. Such a term as latent or subclinical state, which has been objectionable to some investigators, is no longer necessary. It is seen to be a broad state comprising the mild acute and mild chronic conditions. It is preferable to use the more specific designation corresponding to the actual condition. The severe chronic state has had no previous designation.

The concept also explained the various courses in the pathogenesis of these states. Whereas the description thus far has indicated that any one of the several states exists alone, actually conditions are often more complex. Through the usual vicissitudes, particularly over years, the process usually changes in velocity, intensity and even direction. To mention one or two more common of the various eventualities, an acute subsides into a chronic process, or a mild or severe chronic state, once established, constitutes a base on which is superimposed a mild or severe acute process. Undoubtedly in the outbreaks of classic deficiency diseases the severe acute form is very frequently engrafted on a preexisting mild or severe chronic base. But these do not represent all the possible changes in rate, stage and intensity which a process may undergo. It may have a very variable and tortuous course. As a result, a mild or severe acute process in any stage may be seen with a mild or severe chronic form in any stage. These combined states add to the number of categories which must be borne in mind. Thus a deficiency disease may exist in any one of the following states: mild acute, severe acute, mild chronic, severe chronic, as well as mild or severe acute superimposed on mild or severe chronic, each in a particular stage. It cannot be overemphasized that the combined states are very prevalent, perhaps the most prevalent.

Scattered observations in the literature on deficiency diseases are in accord with one or another point in the concept. In addition to the reports already cited on the mild acute state, others have taken cognizance of the chronic state. In describing various forms of rickets, Eliot and Park⁶¹ mentioned early mild, florid and

61. Eliot, Martha M., and Park, E. A.: Rickets, in *Brennemann's Practice of Pediatrics*, Hagerstown, W. F. Prior Company, Inc., 1938, vol. 1, chapter 36, pp. 62-65, 87, 92, 94.

mild chronic. Their description of the course of these respective states may be interpreted in terms of intensity and time.

Furthermore, the literature records the characteristic difference between the acute and chronic forms in response to treatment. Eliot and Park⁶² remark that in one form of rickets the complete cure is slow. It has also been noted that in treatment of polyneuritis in animals, the acute fulminating type disappeared very speedily in a few days, the chronic type very slowly, in fact, only after many months.⁶³

A few investigators have mentioned a chronic state of pellagra in contradistinction to the more dramatic acute form.⁶⁴ Some changes in the tongue in pellagra have been described erroneously as part of the acute process, whereas they were really chronic in nature.⁶⁵ In scurvy produced in animals, Tozer⁶⁶ differentiated the chronic from the acute form on a time basis. She stated that the chronic form varies in severity according to the degree of deprivation of vitamin C. Using a different terminology to express intensity, she described mild and severe degrees for both the acute and chronic forms. Recognizing these various states, Höjer⁶⁷ employed still another nomenclature. Ferrario⁶⁸ and

62. Eliot, Martha M., and Park, E. A.: Rickets, in Brennenmann's Practice of Pediatrics, Hagerstown, W. F. Prior Company, Inc., 1938, vol. 1, chapter 36, p. 65.

63. Vedder, E. B.: Beriberi, New York, William Wood & Co., 1913, chapter 10, pp. 208-209.

64. Titus, S. C.: Oratio de Pellagrae Morbi inter Insubriae Austriacae Agricolae Grassantis Pathologia Viteburg, 1792.⁴⁸ Strambio, Gaetano: Dissertazioni di Gaetano Strambio sulla Pellagra, Milan, Gio Batista Bianchi, 1794, diss. 2, pp. 103-105. Lalesque, F. A.: De la pellagre des Landes, Bull. Acad. Roy. de Med. 1: 440-442, 1836. Morelli, Carlo: La Pellagra nei Suoi Rapporti Medici e Sociali, Florence, Murate, and Monaco, Giorgio Franz, 1856, chapter 2, p. 57.

65. Soler, Luigi: Osservazioni Medico-Pratiche Che Formano la Storia Esatta di una Particolare Malattia Chiamata Pellagra, in Cui Si Espongono I Veri Caratteri, le Differenze, le Cause ed il Metodo Giudicato il Più Utile per Curarla, Venice, Andrea Foglierini, 1791, p. 10. Costallat, A.: Etiologie et prophylaxie de la pellagre, ed. 2, Paris, J.-B. Baillière et Fils, 1868, chapter 3, p. 148. Lombroso, Cesare: Trattato Profilattico e Clinico della Pellagra, Turin, Fratelli Bocca, 1892, part 3, chapter 1, pp. 214, 224. Lussana.⁴⁸

66. Tozer, Frances Mary: On the Histological Diagnosis of Experimental Scurvy, Biochem. J. 13: 445-447, 1918.

67. Höjer, J. Axel: Studies in Scurvy, Acta paediat. 3 (supp.): 7-278, 1924.

68. Ferrario, Carlos V.: La avitaminosis C experimental en el cobayo y las lesiones dentales y del paradencio, Rev. Odont. 29: 206-224 (April) 1941; La avitaminosis C experimental en el cobayo y las lesiones dentales y del paradencio: II. Escorbuto Cronico, ibid. 29: 273-284 (May) 333-349 (June) 1941.

Boyle⁶⁹ also produced acute and chronic scurvy in guinea pigs. Similar observations have been reported on experimental athiaminosis.⁷⁰

The severe acute state is the form on which almost all clinical attention to deficiency diseases has hitherto been focused. Historically this form, presenting a grave problem, was the first to be recognized; consequently the recorded knowledge on its symptoms, signs and pathology predominate in the literature. Similarly in experimental work, where the objective was to demonstrate the existence of new vitamins or to assay foods, animals were suddenly shifted from an optimum natural to a deficient "purified" diet in which every trace of an essential had been as far as possible removed. Naturally the severe acute form of deficiency ensued. A few investigators have given attention to the mild acute state.

In the past the chronic state of deficiency diseases has received only sporadic and scant notice. Paradoxically, however, chronic manifestations have been frequently seen but their relation to nutrition was not recognized. The mild chronic state has been undetected or neglected. Generally the mild acute, mild and severe chronic states, the most common states among the population, have not been recognized and differentiated. The very prevalent combination acute with chronic has not been fully appreciated as such, and the constituent forms have not been distinguished and separated.

Since the chronic state of deficiency diseases has not been commonly recognized, it is worth while to mention some of its characteristics. Its essence is time. For persons this is age. The longer persons live, the more chance they have to incur changes and to have them develop to an advanced state. Consequently chronic

69. Boyle, Paul E.: Experimental Scurvy in Guinea Pigs and Its Relation to Diffuse Alveolar Atrophy in Human Subjects, *Harvard Dent. Rec.* **11**: 5-9 (July) 1937. Boyle, P. E.; Bessey, O. A., and Wolbach, S. B.: Experimental Alveolar Bone Atrophy Produced by Ascorbic Acid Deficiency and Its Relation to Pyorrhea Alveolaris, *Proc. Soc. Exper. Biol. & Med.* **36**: 733-735, 1937. Boyle, Paul E.: Effect of Various Dietary Deficiencies on the Periodontal Tissues of the Guinea Pig and of Man, *J. A. Dent. A.* **28**: 1788-1793 (Nov.) 1941.

70. Prickett, C. O.; Salmon, W. D., and Schrader, G. A.: Histopathology of the Peripheral Nerves in Acute and Chronic Vitamin B₁ Deficiency in the Rat, *Am. J. Path.* **15**: 251-259 (March) 1939. Swank, R. L.: Avian Thiamine Deficiency: A Correlation of the Pathology and Clinical Behavior, *J. Exper. Med.* **71**: 683-702 (May) 1940. Swank, R. L., and Bessey, O. A.: Avian Thiamine Deficiency: 3. Characteristic Symptoms and Their Pathogenesis, *J. Nutrition* **22**: 77-89 (July 10) 1941.

changes are seen with greater frequency and in the latest stages with increasing age. I have noted this in avitaminosis A, ariboflavinosis, aniacinosis and avitaminosis C.

In the past these chronic alterations have been called senile changes with the implication that senility causes them. But senility per se is not responsible for them. That has never been a satisfactory explanation. Not all elderly persons show the changes. On the other hand, they occur in children.⁷¹ Time, not senility, is the essential point. And time does not start the changes, it simply is a dimension over which they progress. They are specific avitaminoses in a state of chronicity, due usually to dietary deficiencies running over a period of years. Their prevalence and severity vary with the number and degree of deficient diets and therefore with the economic level. Most important of all they are reversible, yielding slowly but completely to appropriate therapy.

This rate of response is another characteristic peculiar to the chronic process. Whereas acute changes respond with considerable promptness, chronic changes recede very slowly. In acute changes we are accustomed to expect improvement with dramatic rapidity. Actually, some of rapidity is more apparent than real. For one thing it is a relative matter; the more pronounced the acute, the more spectacular is a given degree of improvement. Often removal of late signs constitutes supposed rapid cure of an acute deficiency. Obviously this is far from complete cure. But it is mainly because the relief of symptoms, the first event, is so prompt as to be striking. If judged solely by freedom from symptoms, the therapeutic response of an acute process is rapid. But when judged by complete restoration of all tissue changes, as seen by the biomicroscope, response in the acute condition is not quite so spectacularly quick as it is reputed. Nevertheless, response is infinitely more rapid in the acute than in the chronic state.

METHODS OF APPRAISAL

With this concept of the various states in mind, it is appropriate to consider the various new methods that have been proposed for use in appraising nutritional

⁷¹ Since it was obviously inappropriate to apply the term senile changes to children, the equally unsuitable name presenile changes was used.

status. They comprise biochemical, microbiologic, biophysical (most of which are functional), special clinical and morphologic, including biomicroscopic. At once it should be stated that they pertain to different aspects of deficiency diseases and yield dissimilar kinds of information.

Most of the biochemical methods are designed to determine the concentration of the vitamins in the blood and urine. One kind of method is based on the reaction of a vitamin to yield a colored or fluorescent substance which, under suitable conditions of intensity and stability, may be estimated. Another kind depends on the reaction of a vitamin with a dye which is carried partially or entirely to completion so that the residual color or end point, respectively, may be determined. For each reaction there are usually several methods, differing only in the size and preparation of the sample and means of estimating the concentration of the vitamin. These reactions are rendered quantitative by colorimetry, fluorimetry and titrimetry, and objective by spectrophotometry or photoelectrometry.

Microbiologic methods depend on the failure of a particular micro-organism to grow in the absence of a specific vitamin. The concentration of the essential is assayed by the degree to which it stimulates growth. Or it is measured by its accelerating action on a biologic process such as fermentation.

For information bearing on the state of nutrition with respect to an essential, the biochemical and microbiologic methods may be applied in four ways. The concentration of the vitamin in blood is determined on specimens collected before breakfast. For a vitamin that is excreted in the urine, the amount there may be ascertained from one or more specimens collected after an interval of several hours from the last meal or from a twenty-four hour sample. In general, low values for the vitamin in either instance point to a recent diet deficient in the essential. Other procedures comprise measuring the response to a test dose of the vitamin, by determining either its absorption from the blood or its excretion in the urine. Here for both blood and urine the methods differ in the amount of vitamin administered, the number of samples to be taken and the time of drawing them. Usually the blood technic includes initial or pretest, peak and sub-

sequent basal determinations. Most of the excretory methods restricted to the collection of one or a few specimens are designed to cover the period of maximum response; some call for a twenty-four hour sample. These urinary response procedures are the saturation, tolerance or load tests. Low values by the procedures involving response to a test dose indicate not only that the previous dietary intake has been deficient but also that the reservoirs are depleted. These several procedures yield information of different character because they bear on such different aspects as transport, storage, utilization and excretion of the vitamin.

Two of the vitamins also occur in the blood as constituents of coenzymes. Hence concentration of that is also determined by the foregoing types of methods. Also chemical methods are used to determine the accumulation of metabolites in the blood or to detect the presence of an abnormal pigment in the urine as the result of a vitamin deficiency.

Among the biochemical methods on blood, the formation of a blue color when vitamin A is treated with a chloroform solution of antimony trichloride⁷² provides the means for determining vitamin A concentration.⁷³ Oxidation of thiamine to thiochrome and measurement of the intensity of the latter's fluorescence⁷⁴ forms the basis of estimating the thiamine level.⁷⁵ Another method for detecting avitaminosis B₁ depends on the

72. Carr, F. H., and Price, E. A.: Colour Reactions Attributed to Vitamin A, *Biochem. J.* **20**: 497-501, 1926.

73. Lanzing, J. C.: De bepaling van het vitamine A-en het carotinoidengehalte in 1 ccm. à 2 ccm. bloed, *Geneesk. tijdschr. Nederland-Indië* **78**: 3135-3144, 1938. Kimble, M. S.: The Photocolorimetric Determination of Vitamin A and Carotene in Human Plasma, *J. Lab. & Clin. Med.* **24**: 1055-1065, 1939. May, C. D.; Blackfan, K. D.; McCreary, J. F., and Allen, F. H., Jr.: Clinical Studies of Vitamin A in Infants and in Children, *Am. J. Dis. Child.* **59**: 1167-1184 (June) 1940. Abels, J. C.; Gorham, Alice T.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of Gastro-Intestinal Tract; Plasma Vitamin A Levels in Patients with Malignant Neoplastic Disease, Particularly of the Gastro-Intestinal Tract, *J. Clin. Investigation* **20**: 749-764 (Nov.) 1941.

74. Jansen, B. C. P.: A Chemical Determination of Aneurin by the Thiochrome Reaction, *Rec. d. trav. chim. d. Pays-Bas* **55**: 1046-1052 (Nov. 15) 1936; Quantitative Bestimmung von Aneurin, *Ztschr. f. Vitaminforsch.* **7**: 239-244, 1938.

75. Westenbrink, H. G. K., and Jansen, B. C. P.: Determination of Cocarboxylase and Aneurin by the Thiochrome Method: 1. 2. *Acta brev. Neerland. physiol.* **8**: 119-120, 1938. Widenbauer, F.; Huhn, O., and Disselhoff, V.: Ueber den Vitamin-B₁-Gehalt des Bluteserums, *Zentralbl. f. inn. Med.* **60**: 113-118 (Feb. 11) 1939. Ritsert, K.: Die Aneurinbestimmung in kleinen Blutmengen nach dem Thiochromverfahren, *Klin. Wchnschr.* **18**: 852-854 (June 17) 1939; Ueber eine einfache Methode zur quantitativen Bestimmung der Cocarboxylase in Blut und Geweben nach dem Thiochromverfahren, *ibid.* **18**: 1370-1372 (Oct. 21) 1939.

increase in values for bisulfite binding substances⁷⁶ or pyruvic acid⁷⁷ signifying failure in decarboxylation from deficiency in thiamine. Pyruvate curves may be obtained following ingestion of glucose^{77a} which accentuates the metabolic difficulty over a test period.

The level of cocarboxylase (thiamine diphosphate ester or thiamine pyrophosphate, which functions as a coenzyme or carboxylase in conversion of pyruvic acid into carbon dioxide and acetaldehyde) may be determined in three ways: differential solubility of thiochrome and thiochrome pyrophosphate,⁷⁸ enzymatic conversion of cocarboxylase into thiamine⁷⁹ or manometric determination of the carbon dioxide released during an enzymatic process in which pyruvate is the substrate.⁸⁰ Goodhart and Sinclair⁸¹ have pointed out that estimation of thiamine or cocarboxylase in whole blood is not a reliable means of detecting possible deficiency of thiamine. They regard lowered concentration

76. Clift, F. P., and Cook, R. P.: A Method of Determination of Some Biologically Important Aldehydes and Ketones with Special Reference to Pyruvic Acid and Methylglyoxal, *Biochem. J.* **26**:1788-1799, 1932. Wilkins, R. W.; Weiss, Soma, and Taylor, F. H. L.: The Effect and Rate of Removal of Pyruvic Acid Administered to Normal Persons and to Patients With and Without "Vitamin B Deficiency," *Ann. Int. Med.* **12**:938-950 (Jan.) 1939. Wortis, Herman; Goodhart, R. S., and Bueding, Ernest: Cocarboxylase, Pyruvic Acid and Bisulfite Binding Substances in Children, *Am. J. Dis. Child.* **61**:226-230 (Feb.) 1941.

77. Peters, R. A., and Thompson, R. H. S.: Pyruvic Acid as an Intermediary Metabolite in the Brain Tissue of Avitaminous and Normal Pigeons, *Biochem. J.* **28**:916-925, 1934. Lu, G. D.: Studies on the Metabolism of Pyruvic Acid in Normal and Vitamin B₁ Deficient States: I. A Rapid, Specific and Sensitive Method for the Estimation of Blood Pyruvate, *ibid.* **33**:249-254 (Feb.) 1939; Studies on the Metabolism of Pyruvic Acid in Normal and Vitamin B₁ Deficient States: II. Blood Pyruvate Levels in the Rat, Pigeon, Rabbit and Man, *ibid.* **33**:774-778 (May) 1939. Bueding, Ernest, and Wortis, Herman: Stabilization and Determination of Pyruvic Acid in Blood, *J. Biol. Chem.* **133**:585-591 (April) 1940. Wortis, Goodhart and Bueding.⁷⁸ Bueding, Ernest; Wortis, Herman; Stern, Marvin, and Esturonne, Dorothy: Pathological Variations in Blood and Spinal Fluid Pyruvic Acid, *J. Clin. Investigation* **21**:85-89 (Jan.) 1942.

77a. Wortis, Herman; Bueding, Ernest; Stein, M. H., and Jolliffe, Norman: Pyruvic Acid Studies in Wernicke Syndrome, *Arch. Neurol. & Psychiat.* **47**:215-222 (Feb.) 1942.

78. Westenbrink and Jansen.⁷⁵

79. Ritsert, K.: Ueber eine einfache Methode zur quantitativen Bestimmung der Cocarboxylase in Blut und Geweben nach dem Thiochromverfahren.⁷⁵ Widenbauer, F.: Ueber den Cocarboxylase-Gehalt des menschlichen Blutes, *Klin. Wchnschr.* **18**:1392-1394 (Oct. 28) 1939.

80. Goodhart, R. S., and Sinclair, H. M.: The Estimation of Cocarboxylase (Vitamin B₁ Diphosphate Ester) in Blood, *Biochem. J.* **33**:1099-1108 (July) 1939; Deficiency of Vitamin B₁ in Man as Determined by the Blood Cocarboxylase, *J. Biol. Chem.* **133**:11-21 (Jan.) 1940. Goodhart, Robert: A Revaluation of the Method Described by Goodhart and Sinclair for the Determination of Blood Cocarboxylase Values, *ibid.* **135**:77-84 (Aug.) 1940. Schlutz, F. W., and Knott, Elizabeth M.: Cocarboxylase Content of Blood of Infants and of Children, *Am. J. Dis. Child.* **61**:231-236 (Feb.) 1941. Wortis, Goodhart and Bueding.⁷⁶

81. Goodhart and Sinclair: The Estimation of Cocarboxylase (Vitamin B₁ Diphosphate Ester) in Blood.⁸⁰

of thiamine in the plasma as furnishing more trustworthy evidence.

For determination of nicotinic acid or nicotinamide in the blood, the reaction of these substances with an aromatic amine and cyanogen bromide⁸² provides several methods.⁸³

A number of chemical methods have been devised for assaying ascorbic acid in the plasma,⁸⁴ most of them based on the reduction of 2:6 dichlorophenol-indophenol,⁸⁵ a few of methylene blue.⁸⁶ The applica-

82. Swaminathan, M.: A Chemical Method for the Estimation of Nicotinic Acid in Biological Materials, *Indian J. M. Res.* **26**: 427-434 (Oct.) 1938. Bandier, E., and Hald, J.: A Colorimetric Reaction for the Quantitative Estimation of Nicotinic Acid, *Biochem. J.* **33**: 264-271 (Feb.) 1939.

83. Ritsert, K.: Zur quantitativen Nicotinsäure- und Nicotinsäureamid Bestimmung im Harn, im Gewebe und im Blut, *Klin. Wchnschr.* **18**: 934-936 (July 8) 1939. Pearson, P. B.: The Nicotinic Acid Content of the Blood of Mammalia, *J. Biol. Chem.* **129**: 491-494 (Aug.) 1939. Euler, H. v., and Schlenk, F.: Nicotinsäureamid und Co-Zymase im Blut, *Klin. Wchnschr.* **18**: 1109-1111 (Aug. 19) 1939. Melnick, Daniel, and Field, Henry, Jr.: Determination of Nicotinic Acid in Biological Material by Means of Photoelectric Colorimetry, *J. Biol. Chem.* **134**: 1-16 (June) 1940. Melnick, Daniel, and Field, Henry, Jr.: Chemical Determination of Nicotinic Acid: Inhibitory Effect of Cyanogen Bromide upon the Aniline Side Reactions, *J. Biol. Chem.* **135**: 53-58 (Aug.) 1940. Melnick, Daniel; Robinson, W. D., and Field, Henry, Jr.: Factors Affecting the Concentration and Distribution of Nicotinic Acid in the Blood, *J. Biol. Chem.* **136**: 157-166 (Oct.) 1940. Field, Henry, Jr.; Melnick, Daniel; Robinson, W. D., and Wilkinson, C. F.: Studies of the Chemical Diagnosis of Pellagra (Nicotinic Acid Deficiency), *J. Clin. Investigation* **20**: 379-386 (July) 1941.

84. Farmer, C. J., and Abt, A. F.: Ascorbic Acid Content of Blood, *Proc. Soc. Exper. Biol. & Med.* **32**: 1625-1629 (June) 1935. Abt, A. F.; Farmer, C. J., and Epstein, I. M.: Normal Cevitamic (Ascorbic) Acid Determinations in Blood Plasma and Their Relationship to Capillary Resistance, *J. Pediat.* **8**: 1-19 (Jan.) 1936. Farmer, C. J., and Abt, A. F.: Titration of Plasma Ascorbic Acid as a Test for Latent Avitaminosis C, *Nutrition: The Newer Diagnostic Methods, Proceedings of the Round Table on Nutrition and Public Health, Sixteenth Annual Conference of the Milbank Memorial Fund, March 29-31, 1938, pp. 114-130; Determination of Reduced Ascorbic Acid in Small Amounts of Blood, Proc. Soc. Exper. Biol. & Med.* **34**: 146-150 (March) 1936. Farmer, C. J.: Vitamin C Analysis in Relation to Clinical Problems, *Quart. Bull. Northwestern University Medical School* **14**: 220-235 (Nov. 4) 1940. Mindlin, R. L., and Butler, A. M.: The Determination of Ascorbic Acid in Plasma: A Macro-method and Micromethod, *J. Biol. Chem.* **122**: 673-686 (Feb.) 1938. Wiehl, Dorothy G., and Kantorovitz, Myron: Medical Evaluation of Nutritional Status: XI. An Analysis of Sources of Errors in the Photometric Macromethod of Determining Ascorbic Acid in Plasma, *Milbank Memorial Fund Quart.* **20**: 178-206 (April) 1942. Kruse,⁸⁰ Butler, A. M., and Cushman, M.: Distribution of Ascorbic Acid in Blood and Its Nutritional Significance, *J. Clin. Investigation* **19**: 459-467 (May) 1940.

85. Tillmans, J.; Hirsch, P., and Hirsch, W.: Das Reduktionsvermögen pflanzlicher Lebensmittel und seine Beziehung zum Vitamin C.: I. Der reduzierende Stoff des Citronensaftes, *Ztschr. f. Unters. d. Lebensm.* **63**: 1-21 (Jan.) 1932.

86. Lund, Helge, and Lieck, Herbert: Quantitative Bestimmung von Ascorbinsäure im Blutserum, *Klin. Wchnschr.* **16**: 555-557 (April 17) 1937. Widenbauer, F., and Schneider, E.: Die Bestimmung von reduzierter und gesamt-Ascorbinsäure im Blutplasma, *ibid.* **17**: 1694-1695 (Nov. 26) 1938. Zimmermann, Wilhelm: Studie über die photometrische Vitamin C-Bestimmung mit der Methylenblaumethode, *ibid.* **17**: 1728-1731 (Dec. 3) 1938. Lund, Helge, and Trier, Erik: 2. Eine neue Mikro-Methylenblaumethode zur quantitativen Bestimmung der Ascorbinsäure im Blutserum, *ibid.* **18**: 80-82 (Jan. 21) 1939.

tion of these methods in various procedures has already been reviewed.⁸⁷ During deproteinization of whole blood, ascorbic acid is readily oxidized to dehydroascorbic acid which does not react with 2,6 dichlorophenol-indophenol; and the measures thus far proposed to prevent or reverse the oxidation have made the determination of ascorbic acid in whole blood with that dye a difficult and unsatisfactory undertaking. A new method^{87a} comprising oxidation of ascorbic acid to dehydroascorbic acid and formation of a colored 2,4-dinitrophenylhydrazine derivative has recently been devised for determination of ascorbic acid in whole blood.

Methods for determining calcium,⁸⁸ phosphorus and phosphatase⁸⁹ levels are well known. Disturbances in these components are associated with rickets.

Plasma or serum proteins may be determined by a convenient colorimetric method.⁹⁰ The significance of alterations in these blood constituents, particularly albumin, has been described at length.⁹¹

Nutritional anemia due to iron deficiency is microcytic and hypochromic in type. Although microcytosis may occur alone, diminution in hemoglobin concentration

87. Smith, S. L.: Human Requirements of Vitamin C, *J. A. M. A.* **111**:1753-1764 (Nov. 5) 1938.

87a. Roe, J. H., and Kuether, C. A.: The Determination of Ascorbic Acid in Whole Blood and Urine Through the 2,4-Dinitrophenylhydrazine Derivative of Dehydroascorbic Acid, *J. Biol. Chem.* **147**: 399-407 (Feb.) 1943.

88. Clark, E. P., and Collip, J. B.: Tisdall Method for Determination of Blood Serum Calcium with Suggested Modification, *J. Biol. Chem.* **63**: 461-464 (March) 1925.

89. Bodansky, Aaron: Notes on the Determination of Serum Inorganic Phosphate and Serum Phosphatase Activity, *J. Biol. Chem.* **120**:167-175 (Aug.) 1937; Notes on the Determination of Serum Inorganic Phosphate and Serum Phosphatase Activity, *Am. J. Clin. Path., Technical Supplement* **7**:51-59 (Sept.) 1937. Fiske, C. H., and Subbarow, Y.: Colorimetric Determination of Phosphorus, *J. Biol. Chem.* **66**: 375-400 (Dec.) 1925.

90. Kingsley, G. R.: The Determination of Serum Total Protein, Albumin and Globulin by the Biuret Reaction, *J. Biol. Chem.* **131**: 197-200 (Nov.) 1939; A Rapid Method for the Separation of Serum Albumin and Globulin, *ibid.* **133**:731-735 (May) 1940; The Direct Biuret Method for the Determination of Serum Proteins: Simplification and Improvements Applied to Photoelectric and Visual Colorimetry, to be published. Robinson, H. W., and Hogden, Corinne, G.: The Biuret Reaction in the Determination of Serum Proteins: I. A Study of the Conditions Necessary for the Production of a Stable Color Which Bears a Quantitative Relationship to the Protein Concentration, *J. Biol. Chem.* **135**:707-725 (Sept.) 1940; II. Measurements Made by a Duboscq Colorimeter Compared with Values Obtained by the Kjeldahl Procedure, *ibid.* **135**:727-731 (Sept.) 1940.

91. Youmans, J. B.: The Diagnosis of Nutritional Edema with Particular Reference to the Determination of Plasma Proteins and Consideration of Their Behavior, Nutrition; The Newer Diagnostic Methods, Proceedings of the Round Table on Nutrition and Public Health, New York, Milbank Memorial Fund, 1938, pp. 166-173.

of the blood is usually an early sign. In the comprehensive examination in private practice or the hospital, a complete hematologic examination is desirable. But in surveys on a large scale the objectives and possible results must be weighed against the limitations in time and personnel and the magnitude of the work. It is doubtful that it would be justifiable to conduct a thousand blood counts when only a few will yield low values. Rather, determination of hemoglobin concentration would seem to be sufficient for most surveys. The results from surveys demonstrate the usefulness and adequacy of this single procedure.⁹²

Here is a technic known for a long time but too often neglected, or conducted by instruments capable of revealing only wide abnormalities and yielding such errors that they could not reveal slight deviations or reported in terms of variable standards,⁹³ with variable allowance for normal range. Osgood⁹⁴ has admonished that "all hemoglobin estimations should be reported in grams per hundred cubic centimeters and the method used should be stated. Otherwise the great variation (13.8 to 17.3) in the number of grams of hemoglobin taken as 100 per cent in different methods and the enormous differences in the accuracy of the methods will make correct interpretation of the results impossible."

Furthermore, in view of indications from other deficiency diseases, perhaps more consideration should be given to slight or marginal changes in hemoglobin concentration. Some agreement on standards, recognition that one level as a standard will not suffice for all ages⁹⁵ and perhaps narrowing of the present wide range accepted as normal are items in need of consideration. Moreover, to remove errors inherent in most

92. Abbott, O. D., and Ahmann, C. F.: Nutritional Anemia and Its Prevention, Bull. 328, University of Florida Agricultural Experiment Station, 1938; Iron Deficiency in Anemia in Children, *Am. J. Dis. Child.* **58**: 811-816 (Oct.) 1939. Mackay, H. M. M., and Goodfellow, L.: Nutritional Anemia in Infancy with Special Reference to Iron Deficiency, Medical Research Council, Special Report Series, No. 157, London, His Majesty's Stationery Office, 1931.

93. Haden, R. L.: Principles of Hematology, Philadelphia, Lea & Febiger, 1939, chapter 4, p. 58.

94. Osgood, E. E.: A Textbook of Laboratory Diagnosis, ed. 3, Philadelphia, Blakiston Company, 1940, chapter 6, p. 177.

95. Wiehl, Dorothy G.: Medical Evaluation of Nutritional Status: III. Hemoglobin and Erythrocyte Values for Adolescents in High Income Families, *Milbank Memorial Fund Quart.* **19**: 45-71 (Jan.) 1941.

instruments, the method should be performed whenever possible on a photoelectric colorimeter.

For assaying the vitamins in urine, the biochemical methods are based mostly on the same reactions as in blood. In the estimation of thiamine the thiochrome⁹⁶ or diazotized P-aminoaceto-phenone reactions is utilized.⁹⁷ Riboflavin excreted as uroflavin is measured by a fluorometric method.⁹⁸ Nicotinic acid derivatives may be determined by their reaction with cyanogen bromide

96. Westenbrink, H. G. K., and Goudsmit, J.: Determination of Aneurin (Vitamin B₁) by the Thiochrome Reaction, *Rec. trav. chim. d. Pays-Bas* **56**:803-810, 1937; Chemical Method for Determination of Vitamin B₁ in Urine, *Nederl. tijdschr. v. geneesk.* **81**:2632-2639 (June 5) 1937. Karrer, W.: Zur Bestimmung von Vitamin B₁ im menschlichen Harn, *Helvet. chim. Acta* **20**:1147-1155 (Nov. 5) 1937. Widenbauer, F.; Huhn, P., and Becker, G.: Chemischer Nachweis und Ausscheidung von Vitamin B₁ im Harn, *Ztschr. f. ges. exper. Med.* **101**:178-186, 1937. Ritsert, K.: Zur Aneurinbestimmung im Harn nach der Janssenschen Thiochrommethode, *Deutsche med. Wchnschr.* **64**:481-484 (April 1) 1938. Jolliffe, Norman; Goodhart, Robert; Gennis, J., and Cline, J. K.: The Experimental Production of Vitamin B₁ Deficiency in Normal Subjects: The Dependence of the Urinary Excretion of Thiamine on the Dietary Intake of Vitamin B₁, *Am. J. M. Sc.* **198**:198-211 (Aug.) 1939. Widenbauer, F.; Huhn, O., and Ellinger, R.: Ueber die Vitamin B₁-Bestimmung im Harn, *Ztschr. f. d. ges. exper. Med.* **105**:138-144, 1939. Hennessy, D. J., and Cerecedo, L. R.: The Determination of Free and Phosphorylated Thiamine by a Modified Thiochrome Assay, *J. Am. Chem. Soc.* **61**:179-183 (Jan.) 1939. Ferrebee, J. W., and Carden, G. A.: A Procedure for the Routine Determination of Vitamin B₁ in Urine, *J. Lab. & Clin. Med.* **25**:1320-1324 (Sept.) 1940. Carden, G. A.; Province, W. D., and Ferrebee, J. W.: Clinical Experiences with the Measurement of the Urinary Excretion of Vitamin B₁, *Proc. Soc. Exper. Biol. & Med.* **45**:1-5 (Oct.) 1940. Wang, Y. L., and Harris, L. J.: Methods for Assessing the Level of Nutrition of the Human Subject: Estimation of Vitamin B₁ in Urine by the Thiochrome Test, *Biochem. J.* **33**:1356-1369 (Aug.) 1939. Wang, Y. L., and Yudkin, John: Assessment of the Level of Nutrition: Urinary Excretion of Aneurin at Varying Levels of Intake, *Biochem. J.* **34**:343-352 (March) 1940. Najjar, V. A., and Holt, L. E., Jr.: Studies in Thiamine Excretion, *Bull. Johns Hopkins Hosp.* **67**:107-124 (Aug.) 1940. Hennessy, D. J.: Chemical Methods for the Determination of Vitamin B₁, *Ind. Eng. Chem. Anal. Ed.* **13**:216-218, 1941.

97. Prebluda, H. J., and McCollum, E. V.: A Chemical Reagent for Thiamine, *J. Biol. Chem.* **127**:495-503 (Feb.) 1939. Melnick, Daniel, and Field, Henry, Jr.: Chemical Determination, Stability and Form of Thiamine in Urine, *ibid.* **130**:97-107 (Sept.) 1939. Melnick, Daniel; Field, Henry, Jr., and Robinson, W. D.: A Quantitative Chemical Study of the Urinary Excretion of Thiamine by Normal Individuals, *J. Nutrition* **18**:593-610 (Dec.) 1939. Robinson, W. D.; Melnick, Daniel, and Field, Henry, Jr.: Urinary Excretion of Thiamine in Clinical Cases and the Value of Such Analyses in the Diagnosis of Thiamine Deficiency, *J. Clin. Investigation* **19**:399-408 (March) 1940. Hennessy, D. J.⁹⁶ Melnick, Daniel, and Field, Henry, Jr.: Thiamine Clearance as Index of Nutritional Status, *J. Nutr.* **24**:131-138 (Aug.) 1942. Melnick, Daniel: Vitamin B₁ (Thiamine) Requirement of Man, *J. Nutr.* **24**:139-151 (Aug.) 1942.

98. Ferrebee, J. W.: The Urinary Excretion of Riboflavin, *J. Clin. Investigation* **19**:251-256 (Jan.) 1940. Najjar, V. A.: Fluorometric Determination of Riboflavin in Urine and Other Biological Fluids, *J. Biol. Chem.* **141**:355-364 (Nov.) 1941. Najjar, V. A., and Holt, L. E., Jr.: Riboflavin Excretion Test as a Measure of Riboflavin Deficiency in Man, *Bull. Johns Hopkins Hosp.* **69**:476-481 (Nov.) 1941.

in the presence of a suitable amine.⁹⁹ Another method for detecting aniacinosis depends on the appearance of a fluorescent substance.¹⁰⁰ Several methods for determination of vitamin C, based on the reduction of 2:6 dichlorophenolindophenol¹⁰¹ or methylene blue,¹⁰² vary in technical points and procedures for appraising the state of vitamin C nutrition. A very complete literature on this has been reviewed.⁸⁷

99. Swaminathan, M.: Urinary Excretion of Nicotinic Acid, *Indian J. M. Res.* **27**: 417-428 (Oct.) 1939. Bandier, E.: Quantitative Estimation of Nicotinic Acid in Urine, *Biochem. J.* **33**: 1787-1793 (Nov.) 1939. Harris, L. J., and Raymond, W. D.: Assessment of the Level of Nutrition: A Method for the Estimation of Nicotinic Acid in Urine, *Biochem. J.* **33**: 2037-2051 (Dec.) 1939. Rosenblum, L. A., and Jolliffe, Norman: Application to Urine of Bandier and Hold's Method for Determination of Nicotinic Acid, *J. Biol. Chem.* **134**: 137-141 (June) 1940. Melnick, Daniel, and Field, Henry, Jr.: Determination of Nicotinic Acid in Biological Materials by Means of Photoelectric Colorimetry, *ibid.* **134**: 1-16 (June) 1940. Melnick, Daniel; Robinson, W. D., and Field, Henry, Jr.: Influence of the Excretion of Other Pyridine Compounds upon the Interpretation of the Urinary Nicotinic Acid Values, *ibid.* **136**: 131-144 (Oct.) 1940; Urinary Excretion of Nicotinic Acid and Its Derivatives by Normal Individuals, *ibid.* **136**: 145-156 (Oct.) 1940. Perlzweig, W. A.; Levy, E. D., and Sarett, H. P.: Nicotinic Acid Derivatives in Human Urine and Their Determination, *ibid.* **136**: 729-745 (Dec.) 1940. Perlzweig, W. A.; Sarett, H. P., and Margolis, L. H.: A Test for Nicotinic Acid Deficiency in Man, *J. A. M. A.* **115**: 28-30 (Jan. 3) 1942. Ritsert.⁸⁸ Euler and Schlenk.⁸⁸ Field, Melnick, Robinson and Wilkinson.⁸⁸

100. Najjar, V. A., and Wood, R. W.: Presence of a Hitherto Unrecognized Nicotinic Acid Derivative in Human Urine, *Proc. Soc. Exper. Biol. & Med.* **44**: 386-390 (June) 1940. Najjar, V. A., and Holt, L. E., Jr.: The Excretion of Specific Fluorescent Substances in the Urine in Pellagra, *Science* **63**: 20-21 (Jan. 3) 1941. Najjar, V. A.; Stein, H. J.; Holt, L. E., Jr., and Kabler, C. V.: Excretion of Specific Fluorescent Substances in Urine in Experimental Nicotinic Acid Deficiency, *J. Clin. Investigation* **21**: 263-267 (May) 1942. Najjar, V. A.; Scott, D. B. M., and Holt, L. E., Jr.: Observations on the Nature and Properties of the Fluorescent Factor F₂, *Science* **67**: 537-538 (June 11) 1943. Huff, J. W., and Perlzweig, W. A.: The Probable Identity of Najjar and Holt's Fluorescent Substance, F₂, *Science* **67**: 538-539 (June 11) 1943.

101. Harris, L. J.; Ray, S. N., and Ward, A.: The Excretion of Vitamin C in Human Urine and Its Dependence on the Dietary Intake, *Biochem. J.* **27**: 2011-2015, 1933. Harris, L. J., and Ray, S. N.: Diagnosis of Vitamin C Subnutrition by Urine Analysis, with a Note on the Antiscorbutic Value of Human Milk, *Lancet* **1**: 71-77 (Jan. 12) 1935. Abbasy, M. A.; Harris, L. J.; Ray, S. N., and Marrack, J. R.: Diagnosis of Vitamin C Subnutrition by Urine Analysis: Quantitative Data, *ibid.* **2**: 1399-1405 (Dec. 21) 1935. Harris, L. J.; Abbasy, M. A.; Yudkin, John, and Kelly, Simon: Vitamins in Human Nutrition: Vitamin C Reserves of Subjects of the Voluntary Hospital Class, *ibid.* **1**: 1488-1490 (June 27) 1936. Evelyn, K. A.; Malloy, Helga T., and Rosen, Charles: The Determination of Ascorbic Acid in Urine with the Photoelectric Colorimeter, *J. Biol. Chem.* **126**: 645-654 (Dec.) 1938. Beasey, O. A.: A Method for the Determination of Small Quantities of Ascorbic Acid and Dehydroascorbic Acid in Turbid and Colored Solutions in the Presence of Other Reducing Substances, *ibid.* **126**: 771-784 (Dec.) 1938. Sendroy, J. Jr., and Miller, B. F.: Renal Function as Factor in Urinary Excretion of Ascorbic Acid, *J. Clin. Investigation* **18**: 135-140 (Jan.) 1939. Harris, L. J.: Vitamin C Levels of School-Children and Students in War-Time, *Lancet* **1**: 642-644 (May 30) 1942.

102. Lund, H.: Eine quantitative und spezifische Methode zur Ascorbinsäure-titration im Harn und zur Bestimmung des Schwellenwertes, *Klin. Wchnschr.* **16**: 1085-1087 (July 31) 1937.

Of the microbiologic methods on blood, the estimation of thiamine concentration¹⁰³ was based on the necessity of this substance for growth of the fungus *Phycomyces blakesleanus*.¹⁰⁴ That thiamine was found to increase the rate of fermentation¹⁰⁵ was utilized in another type of method.¹⁰⁶ The indispensability of riboflavin for lactic acid bacteria¹⁰⁷ led to a method for determining the concentration of this vitamin in blood by use of *Lactobacillus casei*.¹⁰⁸ Factor V, a growth factor for *Hemophilus parainfluenzae*, has been shown to be replaceable by two coenzymes (cozymase or codehydrogenase) which contain nicotinamide. Hence this micro-organism has been used to measure the cozymase content of the blood.¹⁰⁹ But it is stated that determina-

103. Meiklejohn, A. P.: The Estimation of Vitamin B₁ in Blood by a Modification of Schopfer's Test, *Biochem. J.* **31**: 1441-1451 (Sept.) 1937. Rowlands, E. N., and Wilkinson, J. F.: The Clinical Significance and Estimation of Blood Vitamin B₁, *Brit. M. J.* **2**: 878-883 (Oct. 29) 1938. Sinclair, H. M.: The Estimation of Vitamin B₁ in Blood, *Biochem. J.* **32**: 2185-2199 (Dec.) 1938; The Estimation of Vitamin B₁ in Blood: II. A Further Modification of Meiklejohn's Method, *ibid.* **33**: 2027-2036 (Dec.) 1939.

104. Schopfer, W. H.: Recherches sur l'emploi possible d'un végétal pour la vitamine B₁: Essai d'étalonnage, *Bull. Soc. chim. biol.* **17**: 1097-1109 (July-Aug.) 1935; Etude sur les facteurs de croissance: Action de la vitamine cristallisée B₁ et de l'extrait de germe de blé sur *Rhizopus* et d'autres Mucorinées, *Ztschr. f. Vitaminforsch.* **4**: 187-206 (July) 1935.

105. Schultz, A.; Atkin, L., and Frey, C. N.: A Fermentation Test for Vitamin B₁, *J. Am. Chem. Soc.* **59**: 948-949 (May) 1937.

106. Atkin, Lawrence; Schultz, A. S., and Frey, C. N.: Ultramicrodetermination of Thiamine by the Fermentation Method, *J. Biol. Chem.* **129**: 471-476 (Aug.) 1939. Goodhart, Robert: The Thiamine Content of Human Blood and Urine as Determined by the Fermentation Method, *J. Clin. Investigation* **20**: 625-630 (Nov.) 1941. Schultz, A. S.; Atkin, Lawrence, and Frey, C. M.: Determination of Vitamin B₁ by Yeast Fermentation Method, *Ind. Eng. Chem. Anal. Ed.* **14**: 35-39, 1942. Gorham, Alice T.; Abels, J. C.; Robins, Annette, L., and Rhoads, C. P.: Measurement and Metabolism of Thiamin and of Pyrimidine Stimulating Yeast Fermentation Found in Blood Cells and Urine of Normal Individuals, *J. Clin. Investigation* **21**: 161-176 (March) 1942.

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108. Snell, E. E., and Strong, F. M.: A Microbiological Assay for Riboflavin, *Indust. & Engin. Chem., Anal. Ed.* **11**: 346-350 (June) 1939. Strong, F. M.; Feeney, R. E.; Moore, Barbara, and Parsons, Helen T.: The Riboflavin Content of Blood and Urine, *J. Biol. Chem.* **137**: 363-372 (Jan.) 1941. Axelrod, A. E.; Spies, T. D., and Elvehjem, C. A.: Riboflavin Content of Blood and Muscle in Normal and in Malnourished Humans, *Proc. Soc. Exper. Biol. & Med.* **46**: 146-149 (Jan.) 1941.

109. Kohn, H. I.: The Concentration of Coenzyme-like Substance in Blood Following the Administration of Nicotinic Acid to Normal Individuals and Pellagrins, *Biochem. J.* **32**: 2075-2083 (Dec.) 1938. Vilter, R. W.; Vilter, Sue P., and Spies, T. D.: Relationship Between Nicotinic Acid and a Codehydrogenase (Cozymase) in Blood of Pellagrins and Normal Persons, *J. A. M. A.* **112**: 420-422 (Feb. 4) 1939. Determination of the Codehydrogenases I and II (Cozymase) in the Blood of Diabetics in Severe Acidosis, *Am. J. M. Sc.* **197**: 322-326 (March) 1939. von Euler, V., and Schlenk, F.: Nicotinsäureamid und Cozymase im Blut, *Klin. Wchnschr.* **18**: 1109-1111 (Aug. 19) 1939. Kohn, H. I., and Bernheim, F.: The Blood V Factor (Coenzyme) Level in Normal and Pathological Subjects, *J. Clin. Investigation* **18**: 585-591 (Sept.) 1939. Axelrod, Gordon and Elvehjem.¹¹⁰

tion of coenzyme I offers little diagnostic information in borderline cases of deficiency disease.¹¹⁰ The fermentation test has been used in determining the thiamine content of urine.¹¹¹ Riboflavin in the urine has been estimated by bacterial assay with *L. casei*.¹¹² With dog's urine the growth of *Bacterium paratyphosum* and *H. parainfluenzae* has been used to assay the content of nicotinic acid¹¹³ and factor V respectively.¹¹⁴

In an attempt to simplify the method of estimating tissue saturation with vitamin C, Rotter¹¹⁵ introduced the intradermal test whereby a small amount of dichlorophenol-indophenol dye is injected beneath the skin and the fading time is recorded. The validity and reliability of the test have been questioned, principally because its values do not correspond with plasma levels of vitamin C.¹¹⁶ Recently this skin test was found to

110. Axelrod, A. E.; Gordon, E. S., and Elvehjem, C. A.: The Relationship of the Dietary Intake of Nicotinic Acid to the Coenzyme I Content of Blood, *Am. J. M. Sc.* **199**: 697-705 (May) 1940.

111. Schultz, A. S.; Light, R. F., and Frey, C. N.: Vitamin B₁ Metabolism in Man: Excretion of B₁ in Urine and Feces, *Proc. Soc. Exper. Biol. & Med.* **38**: 404-406 (April) 1938. Schultz, A. S.; Atkin, Lawrence, and Ficy, C. N.: A Method for the Determination of Thiamine and Certain of Its Metabolic Products in Urine, *J. Biol. Chem.* **136**: 713-717 (Dec.) 1940. Pollack, Herbert; Ellenberg, Max, and Dolger, Henry: Clinical Studies on Vitamin B₁ Excretion Determined by the Fermentation Method, *Arch. Int. Med.* **67**: 793-804 (April) 1941. Goodhart.¹⁰⁶ Gorham, Abels, Robins and Rhoads.¹⁰⁸

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114. Pittman, Margaret, and Fraser, H. F.: The Determination of V Factor in the Urine and Tissues of Normal Dogs and of Dogs with Blacktongue by the Use of *Hemophilus Parainfluenzae*, *Pub. Health Rep.* **55**: 915-925 (May 24) 1940.

115. Rotter, H.: Determination of Vitamin C in the Living Organism, *Nature* **139**: 717 (April 24) 1937. Portnoy, Benjamin, and Wilkinson, J. F.: Intradermal Test for Vitamin C Deficiency, *Brit. M. J.* **1**: 328-329 (Feb. 12) 1938.

116. Poncher, H. G., and Stubenrauch, C. H., Jr.: Intradermal Dye Test for Vitamin C Deficiency, *J. A. M. A.* **111**: 302-304 (July 23) 1938. Jetter, W. W.: Correlation Between Blood Ascorbic Acid and the Dichlorophenol-Indophenol Intradermal Test, *Proc. Soc. Exper. Biol. & Med.* **39**: 169-171 (Oct.) 1938. Poulsen, E., and Lieck, H.: Undersøgelser over H. Rotter's Intracutanprøve Paa Mennesker Til Paavising af Vitamin C, *Ugesk. f. læger* **101**: 206-208, 1939.

be more closely related to the urinary excretion test for saturation with vitamin C.¹¹⁷

Similar in principle but different in approach is the suggested procedure of ascertaining vitamin B₁ status by determining the concentration of thiamine in a sample of skeletal muscle obtained by microbiopsy.^{117a}

Biophysical methods have been designed to elicit under stress and to measure by special instruments functional or structural impairments attributed to avitaminoses. Methods for detection of visual dysadaptation to darkness were in use long before they were proposed as a means of recognizing early avitaminosis A.¹¹⁸ Following Fridericia and Holm's experimental production of night blindness in rats on an A-deficient diet,¹¹⁹ Jeans suggested that dysadaptation be used as an index of avitaminosis A.¹²⁰ Several instruments for measuring dark adaptation have been devised.¹²¹ These instruments have been shown to have technical faults and the test itself has been criticized on

117. Banerjee, Sachchidananda, and Guha, B. C.: The Intradermal Test as an Index of Vitamin C Nutrition, *Indian M. Gaz.* **75**: 468-473 (Aug.) 1940.

117a. Carleen, Mildred H.; Weissman, Norman; Owen, P. S., and Ferrebee, J. W.: Subclinical Vitamin Deficiency, *Science* **97**: 47-49 (Jan. 8) 1943.

118. Birch-Hirschfeld, A.: Ueber Nachtblindheit im Kriege, *Arch. f. Ophth.* **92**: 273-340, 1917; Weitere Untersuchungen über Nachtblindheit im Kriege, *Ztschr. f. Augenheilk.* **35**: 57-89, 1917. Adams, Dorothy: Dark Adaptation: A Review of the Literature, Medical Research Council, Special Report Series, No. 127, London, His Majesty's Stationery Office, 1929.

119. Fridericia, L. S., and Holm, E.: Experimental Contribution to the Study of the Relation Between Night Blindness and Malnutrition: Influence of Deficiency of Fat Soluble A Vitamin in the Diet on the Visual Purple in the Eyes of Rats, *Am. J. Physiol.* **73**: 63-78, 1925.

120. Jeans and Zentmire.⁵¹

121. Jeans, P. C.; Blanchard, E. L., and Satterthwaite, F. E.: Dark Adaptation and Vitamin A: Further Studies with the Biophotometer, *J. Pediat.* **18**: 170-194 (Feb.) 1941. Hecht, Selig, and Schlaer, S.: Adaptometer for Measuring Human Dark Adaptation, *J. Optic. Soc. America* **28**: 269-275 (July) 1938. Feldman, J. B.: Practice of Dark Adaptation (review), *Arch. Ophth.* **19**: 882-901 (June) 1938. The Use of the Photometer in Detecting Latent Avitaminosis A, Nutrition: The Newer Diagnostic Methods, Proceedings of the Round Table on Nutrition and Public Health, Sixteenth Annual Conference of the Milbank Memorial Fund (March 29-31) 1938, pp. 63-75. Sloan, Louise L.: Instruments and Technics for the Clinical Testing of Light Sense: I. Review of the Recent Literature, *Arch. Ophth.* **21**: 913-934 (June) 1939; II. Control of Fixation in the Dark Adapted Eye, *ibid.* **22**: 228-232 (Aug.) 1939; III. An Apparatus for Studying Regional Differences in Light Sense, *ibid.* **22**: 233-251 (Aug.) 1939. Pett, L. B.: Vitamin A Deficiency: Its Prevalence and Importance as Shown by a New Test, *J. Lab. & Clin. Med.* **25**: 149-160 (Nov.) 1939. Pett, L. B., and Lipkind, M. K.: Factors Affecting the Pett Visual Test for Vitamin A Deficiency, *Canad. J. Res. (B)* **19**: 99-108 (April) 1941. Wald, George: A Portable Visual Adaptometer, *J. Optic. Soc. America* **31**: 235-238 (March) 1941. Jeans and Zentmire.⁵¹ Hecht.⁵¹

its subjectivity, lack of fixed threshold and standards.¹²² The extensive literature on the subject has been presented.¹²³ Furthermore, under actual field conditions in three surveys the most recent models gave disappointing results, since a single measurement of the visual threshold was found not to be a reliable indicator of mild avitaminosis A.¹²⁴ The fault seems to lie not in the instruments or in their ability to detect dysadaptation but in the inference that dysadaptation appears as a sign of early or mild avitaminosis A. The latter inference has been questioned.⁵⁵

Measurement of capillary resistance to pressure, another biophysical method, has been applied in appraising vitamin C status. Like dysadaptation, capillary fragility was originally described in association with a variety of pathologic states.¹²⁵ In 1914 Hess described tests with positive pressure showing impaired capillary resistance in scorbutic infants.¹²⁶ Using the same procedure and counting petechiae, Göthlin suggested that capillary resistance or fragility be used as a measure of vitamin C status.¹²⁷ Meanwhile, a method for measuring capillary fragility by application of negative pressure had been developed and used in many diseases,

122. Snelling, C. E.: A Study of the Birch-Hirschfeld Photometric Test for Vitamin A Deficiency, *J. Pediat.* **9**: 655-661 (Nov.) 1936. Palmer, C. E., and Blumberg, Harold: The Use of a Dark Adaptation Technic (Biophotometer) in the Measurement of Vitamin A Deficiency in Children, *Pub. Health Rep.* **52**: 1403-1418 (Oct. 8) 1937. Palmer, C. E.: The Dark Adaptation Test for Vitamin A Deficiency, *Am. J. Pub. Health* **28**: 309-315 (March) 1938. Hunt, Eleanor P., and Palmer, C. E.: Medical Evaluation of Nutritional Status: II. Measurement of Visual Dark Adaptation with the Adaptometer, *Milbank Memorial Fund Quart.* **18**: 403-424 (Oct.) 1940.

123. Hunt and Hayden.⁵³

124. Steven, David, and Wald, George: Vitamin A Deficiency: A Field Study in Newfoundland and Labrador, *J. Nutrition* **21**: 461-476 (May) 1941. Yarbrough, M. E., and Dann, W. J.: Dark Adaptometer and Blood Vitamin A Measurements in a North Carolina Nutrition Survey, *J. Nutrition* **22**: 597-607 (July) 1941. Hunt and Hayden.⁵³

125. Koch, C.: Ein Beitrag zur Purpura bei Kindern, *Jahrb. f. Kinderh. u. physisch. Erzieh.* **30**: 403-408, 1889-1890. Rumpel, T.: Aerztlicher Verein im Hamburg, Sitzung vom 15 Juni 1909, München. med. Wchnschr. **56**: 1404, 1909. Leede, C.: Hautblutungen durch Stauung hervorgerufen als diagnostisches Hilfsmittel beim Scharlach, *ibid.* **58**: 293-295 (Feb.) 1911; Zur Beurteilung des Rumpel-Leedeschen Scharlachphänomens, *ibid.* **58**: 1673-1674 (Aug.) 1911. Lewis, Thomas, and Harmer, I. M.: Rupture of Minute Vessels in Skin and Distributions of Cutaneous Haemorrhages and Other Skin Eruptions, *Heart* **18**: 337-355 (Dec.) 1926.

126. Hess, A. F.: Survey—Past and Present, Philadelphia, J. B. Lippincott Company, 1920, chapter 7, p. 212. Hess and Fish.⁵²

127. Göthlin, G. F.: Outline of a Method for the Determination of the Strength of the Skin Capillaries and the Indirect Estimation of the Individual Vitamin C Standard, *J. Lab. & Clin. Med.* **18**: 484-490 (Feb.) 1933; A Method of Establishing the Vitamin C Standard and Requirement of Physically Healthy Individuals.⁵³

but not with reference to vitamin C undernutrition.¹²⁸ Later it was adapted to appraising vitamin C status.¹²⁹

Several investigators have found no correlation between the values for capillary resistance and the plasma concentration or urinary excretion of ascorbic acid.¹³⁰ More important, the method yielded a high degree of variation in values. Its limitations have been fully discussed.¹³¹ It is useful for recognizing somewhat severe acute scurvy. But it does not detect early or mild avitaminosis C, for capillary fragility does not appear in this state.⁵⁸

For many years, tests of neuromuscular response to galvanic stimulation were employed in clinical medicine. Although the method was first applied to adults,¹³² its use was soon limited to the diagnosis of "latent" tetany in infants and children.¹³³ It indicated, therefore, disturbances in calcium or vitamin D, or both. Its wide variability in older children and adolescents and the availability of methods for determining the content of calcium in the blood led to almost complete abandonment of the neuromuscular method.

Morphologic methods include the x-rays, the microscope and the bionicroscope with simple inspection for

128. Hecht, A. F.: Experimentell-klinische Untersuchungen über Hautblutungen im Kindesalter, *Jahrb. f. Kinderh.* **65**: 113-131, 1907. Frontali, Gino: I Capillari nel Bambino: Studi sull'Aspetto Microscopico sulla Resistenza, sulla Permeabilità e sulla Pressione Capillare nel Vivente, *Arch. di pat. e clin. med.* **6**: 1-90 (March) 1927. da Silva Mello, A.: Die Wandresistenz der Blutkapillaren (Eine einfache, klinische Methode zu ihrer genauen Messung), *München. med. Wchnschr.* **76**: 1717-1718 (Oct. 11) 1929. Cutter, I. S., and Marquardt, G. H.: Studies in Capillary Fragility, *Proc. Soc. Exper. Biol. & Med.* **28**: 113-115 (Nov.) 1930. Cutter, I. S., and Johnson, C. A.: Studies on Capillary Fragility: A Device for Study of Capillary Hemorrhage, *J. A. M. A.* **105**: 505-506 (Aug. 17) 1935.

129. Dalldorf, Gilbert: A Sensitive Test for Subclinical Scurvy in Man, *Am. J. Dis. Child.* **46**: 794-802 (Oct.) 1933. Schultz, M. P.: Studies of Ascorbic Acid and Rheumatic Fever: II. Test of Prophylactic and Therapeutic Action of Ascorbic Acid, *J. Clin. Investigation* **15**: 385-391 (July) 1936.

130. Abt, A. F.; Farmer, C. J., and Epstein, I. M.: Normal Cevitamic (Ascorbic) Acid Determinations in Blood Plasma and Their Relationship to Capillary Resistance, *J. Pediat.* **8**: 1-19 (Jan.) 1936. Anderson, G. K.; Hawley, Estelle E., and Stephens, D. J.: Capillary Fragility and Vitamin C, *Proc. Soc. Exper. Biol. & Med.* **34**: 778-782, 1936. Liebmann, James; Wortis, Herman, and Wortis, Ethel: Note on the Lack of Correlation of Capillary Fragility with Vitamin C Content of Blood, Spinal Fluid and Urine, *Am. J. M. Sc.* **196**: 388-392 (Sept.) 1938.

131. Gothlin, G. F.: When Is Capillary Fragility a Sign of Vitamin C Subnutrition in Man? *Lancet* **2**: 703-705 (Sept. 18) 1937. Sloan, R. A.: A Comparison of Methods for Detecting and Grading Sub-clinical Scurvy, *J. Lab. & Clin. Med.* **23**: 1015-1026 (July) 1938.

132. Erb, W.: Zur Lehre von der Tetanie nebst Bemerkungen über die Prüfung der elektrischen Erregbarkeit motorischen Nerven, *Arch. f. Psychiat. u. Nervenkrankh.* **4**: 271-316, 1874.

133. Holmes, J. B.: The Reliability of the Electrical Diagnosis of Tetany with Especial Consideration of the Electrical Value Found in Normal Children, *Am. J. Dis. Child.* **13**: 1-29 (July) 1916.

definite lesions. New aids in the recognition of slight changes in the skeleton in early scurvy by x-ray examination have been furnished.⁵⁴ At the same time it has been pointed out that subperiosteal hemorrhages in infantile scurvy may not be visualized on the roentgenogram until administration of vitamin C induces deposition of calcium salts in the periosteum.¹⁸⁴

According to Eliot and Park¹³⁵ "the x-rays give more accurate information concerning the existence of active or healing rickets than physical examination, but for early diagnosis they have limitations. . . ." Furthermore, it has been shown that there may be conflict of opinion as to the presence or absence of evidence of rickets in individual films.¹⁸⁶

By differential staining and microscopic examination the demonstration of keratinized epithelial cells in the scrapings from the cornea, the nose and the mouth, and in secretions from the trachea, bronchi, kidneys and vagina has been proposed as confirmatory diagnostic evidence in suspected cases of avitaminosis A.¹⁸⁷ It will be noted this procedure was not asserted to be a means of early detection.

Gross and biomicroscopic examination of the conjunctiva, ocular limbus, tongue and gums reveals all forms, degrees and stages of avitaminosis A, ariboflavinosis, aniacinosis and avitaminosis C respectively.¹³⁸ In each specific tissue site selected for observation the pathologic process not only appears early but persists and changes in correspondence with the course of the avitaminosis. Furthermore, the site is readily accessible to observation. Although very much may usually be seen grossly in moderate and severe states, the biomicroscope is exceedingly sensitive in revealing the very early and slight tissue changes. It allows low grade states, whether prolonged or not, to be detected. In fact, it is essential for observation of these states. The slighter the change and the closer

134. Nelson, W. E.; Doughty, W. M., and Mitchell, A. G.: Roentgenographic Visualization of Subperiosteal Hemorrhage in Infantile Scurvy, *J. A. M. A.* **101**: 14-17 (July 1) 1933.

135. Eliot, Martha M., and Park, E. A.: Rickets, in Brenne-mann's Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1938, vol. 1, chapter 36, p. 92.

136. Cooley, T. B., and Reynolds, L.: The Interpretation of X-Ray Films in the Diagnosis of Rickets, *J. Pediat.* **10**: 743-747 (June) 1937.

137. Blackfan, K. D., and Wolbach, S. B.: Vitamin A Deficiency in Infants: A Clinical and Pathological Study, *J. Pediat.* **3**: 679-706 (Nov.) 1933.

138. Kruse, footnotes 55, 57 and 58. Kruse, Sydenstricker, Sebrell and Cleckley.⁵⁴ Sydenstricker, Sebrell, Cleckley and Kruse.⁵⁶

it approaches perfection, the more the microscope is needed. From this examination, status is expressed for both acute and chronic processes, each in terms of stage and degree.

CHOICE OF METHODS

Which kind of method is best? The answer depends on the purpose for which the method is to be used. The outstanding objective is the appraisal of nutritional status in the population, to be conducted in schools, industry, business organizations, private practice, hospitals, public health centers and fields surveys. Certain requirements inherent in this objective must be met. The test for a particular deficiency disease should be simple, easy, quick and reliable. Preferably it should be objective rather than subjective. Practical considerations require that it be feasible. The tests for individual deficiencies should be adaptable to combination in a system of examination which retains all the qualities enumerated. Furthermore, such a system should not require too many instruments or large personnel. When one instrument can be used for several tests there is a distinct advantage. The system must also be applicable to all ages, adults as well as children. No age group should be overlooked. It should be noted that many methods in the past applied exclusively to children. Malnutrition in adults has been a neglected subject. Important as is nutrition in the growth period, it is equally important in the later decades. Recognition of the chronic state gives emphasis to this statement. Finally, in order to characterize malnutrition it is essential not only to detect the occurrence but also to establish the status of each deficiency disease. It is particularly important that the system of evaluation should be effective in detecting the states in which deficiency diseases actually exist most frequently in the population. Most of the deficiency states in this country are chronic, in all degrees and with or without an accompanying mild or severe acute process.¹³⁹ Hence the system should permit detection of all forms, stages and degrees.

The several kinds of tests vary in meeting these requirements. Biochemical and microbiologic methods on blood, despite their usefulness and essentiality for many purposes, have disadvantages for application in

139. Kruse, H. D.: Unpublished observations.

surveys. They are laborious, are time consuming and require a laboratory with trained personnel. Unfortunately too, as a means of appraising nutrition they have very narrow limitations beyond which they are misleading.

In the evolution and recession of an avitaminosis, the change in concentration of a vitamin in the blood and the alteration in tissue state are not synchronous. They are on different time schedules. Blood is the labile transport system. If in the initial attack the tissue were normal and the blood value were low, such a value would be significant. But practically this condition is the least frequent in the general population, indeed relatively unprevalent, and would be found mostly in infants and preschool children. With widespread prevalence of avitaminoses, particularly in the chronic form, and their establishment early in life in most persons, a perfect state in the tissue is relatively infrequent. It should not be forgotten, furthermore, that the biomicroscopic examination of tissue is sensitive in detecting the very early and mild tissue changes, indeed all states. Hence the blood method as a primary screen for the appraisal of vitamin C status has in reality a very limited range of application.

Once chronic changes have appeared—and this is the common eventuality and the most prevalent state—the blood values may be unreliable. The chronic process in the tissue recedes exceedingly slowly, almost infinitesimally, on any sustained improvement in diet and only very slowly under persistent therapy. In contrast, values on the concentration of a vitamin in the blood reflect very sensitively the recent dietary habits¹⁴⁰ as well as other conditioning factors. They may change not only with season¹⁴¹ but also within shorter periods; they may fluctuate. Blood values rise rapidly in reflecting changes in improved intake, such as from seasonal or occasional dietary improvement, but with no noticeable effect in the chronic process in the tissue. A sustained satisfactory blood level resulting from adoption of a satisfactory diet or taking of low potency maintenance tablets, now so popular, is not accompanied by any appreciable improvement in an existing severe chronic pathologic condition in the

140. Milam and Wilkins.⁵⁰

141. Trier, A. E.: Serumascorbinsyreens Aarstidsvariation, Ugesk. f. læger. 100:10-14 (Jan. 6) 1938.

tissue. Potent therapy will produce maximum blood levels and entirely restore bodily saturation in several weeks but will completely repair the slightest chronic tissue lesion only in months. Here a high blood level will be maintained over the many months while the tissue lesion is receding but is, of course, still abnormal. Temporarily or consistently, therefore, the blood values may, under these several circumstances, be moderate or high without demonstrable recession in the existing chronic lesion. In any of these instances the blood value would indicate a satisfactory nutritional status while the tissue would be pathologic. Manifestly, appraisal from the blood value alone would be entirely misleading.

It should be clear that there is no necessary high correlation between data derived by different methods on the same deficiency disease. They provide information on different aspects and states of the disorder. Unfortunately, this fact has not been appreciated. Rather, it has been thought that various methods applied to the same deficiency disease should yield similar data. On this basis it has become the practice to test the validity of a method by comparing its results with blood values. This procedure is entirely unsound. When it is remembered that blood values shift rapidly and may fluctuate intermittently, while tissue changes very slowly, there should be no expectation of identical results.

An example demonstrating these points is particularly revealing. With the development of accurate methods for determining the concentration of ascorbic acid in blood and urine, analyses have been conducted on these fluids, after a fasting period or a test dose, as a means of appraising vitamin C status. There has been a strong trend toward general acceptance of the results from these procedures as the true index of bodily status with respect to vitamin C. Indeed, the reliability of other methods of appraisal has been gaged by comparison with blood values as the criterion. Yet Greenberg, Rinehart and Phatak¹⁴² cautioned ". . . the estimation of the reduced plasma ascorbic acid is only a measure of the immediate nutritive or metabolic level relative to vitamin C and is dependent

142. Greenberg, L. D.; Rinehart, J. F., and Phatak, N. M.: Studies on Reduced Ascorbic Acid Content of the Blood Plasma, *Proc. Soc. Exper. Biol. & Med.* **35**:135-139 (Oct.) 1936.

on recent dietary habits to a large degree. Although it is an index of the vitamin C nutrition at the time of the test, in a single case a low level does not imply tissue injury or scurvy (either clinical or subclinical). The latter results from the operation of suboptimal or low metabolic levels over some period of time. Conversely, a good or high level would not indicate that deficiency had not operated to produce tissue injury in the past."

In line with this statement, Crane and Woods,¹⁴⁹ studying an acute outbreak of scurvy in children by comparing gingival condition with ascorbic acid concentration in plasma both in the autumn and in the following spring, found that 7 of 17 children with consistently high ascorbic acid values on both occasions had gingival inflammation at one or the other examination, while 14 of 25 children with inflammation of at least six months' duration had high values on one or the other occasion. A similar comparison of ascorbic acid values with the states of the gingival lesions which I⁵⁸ conducted in a low income group, with a more sensitive method of detecting and more rigid criteria of rating pathologic conditions in the gums, revealed an even less constant relationship. These results, far from demonstrating that the blood level is a trustworthy criterion for comparison of other methods, show that it has serious restrictions as a method for appraising vitamin C status. Determination of the excretory level and bodily saturation tests, whether from serial analyses on blood or on urine, also have these limitations.

In several hands, routine examination by the biophysical methods has failed completely to detect early or even moderately intense avitaminosis.¹⁴³ Either the disturbances, e. g. dysadaptation and petechiae, are not pronounced enough in their early stages to be detected or they are late manifestations.

The limitations of the blood, urine and biophysical methods for evaluation of nutritional status do not discredit them. Used appropriately, each kind of method has value. Each has its place; each presents information on a different aspect of nutrition. The numerous articles in the literature describing studies by blood and urine methods attest their utility. For following the

143. Steven and Wald.¹²⁴ Yarbrough and Dann.¹²⁴ Hunt and Hayden.⁵⁰ Kruse.⁵⁰

quick reflection of dietary habits in the body, for secondary screening of persons without avitaminotic tissue changes, for specific metabolic studies, the blood or urine technic is the method of election. Similarly, for studying dysadaptation and night blindness, the adaptometer is the proper instrument.

The methods which embody gross and biomicroscopic examination of specific tissues for characteristic morphologic changes—the eyes for avitaminosis A and ariboflavinosis, the gums for avitaminosis C and the tongue for aniacinosis—meet most requirements for appraising nutritional status. Particularly they permit both the acute and chronic forms of tissue change in any stage and degree to be detected. True, if the tissue is normal, it is possible that the blood values may be low. This situation, however, is the least frequent in the general population. Such a circumstance would be encountered most often in infants and preschool children. But the biomicroscopic system as a primary screen is so sensitive in detecting the very early or mild form that routine blood values as a secondary screen would add information in only a comparatively small number of instances.

There are still some gaps in the several systems for appraising nutrition. Despite the lack of a few tests, there are now enough for application. Considering the rapid progress in this field, it is to be expected that before long the systems will be rounded out.

PREVALENCE OF MALNUTRITION

Obviously the recorded prevalence of malnutrition depends on the concept, criteria and means of recognizing it. In the past it has been judged by physical measurements or by presence of assorted gross signs, including those of the severe acute type of deficiency disease. Neither method has revealed any considerable prevalence of malnutrition. It is very misleading to rely on them for evidence on the amount of malnutrition. Simple inspection is not sufficiently sensitive to detect mild deficiency states, whether acute or chronic. Most of the chronic changes, even when severe, have not been recognized as specific characteristics of deficiency diseases. These conditions constitute the largest part of malnutrition.

Already the gross and biomicroscopic methods of examining tissue have yielded results indicating a high

prevalence of deficiency states.¹³⁹ Even in high economic groups there are few people in absolutely perfect nutrition. Yet these results are not surprising. Very few persons have consistently followed throughout life a diet satisfactory in all essentials, escaped the many other causes contributing to a deficiency state or had complete recovery from any impairment of their nutrition. The older the person, the more opportunity he has had for some dietary lapse or adverse influence. Then too the standard of perfection in the tissue is very exacting. And the biomicroscopic method is so sensitive that it is capable of detecting slight abnormalities. From all these considerations, the high prevalence of deficiency diseases is not unexpected.

Taken by and large, most of the malnutrition is chronic, with or without mild acute; some of it is mild, but much is rather severe.¹³⁹ This condition too is understandable. Often faulty diets persist for many years.

Some broad generalizations can be drawn about the several states in relation to factors affecting them. Like prevalence, the status of a deficiency disease is influenced by economic level, geographic region and age as well as by lesser environmental factors. Of these three it may be seen that the first two are indexes of the number, nature and degree of dietary deficiencies. Age is again the time factor. In the lower economic groups, deficiency diseases tend to be more numerous, more severe and more advanced than in the higher economic groups. In geographic regions where a particular deficiency disease is endemic the severe acute form is common; in other regions it is rarely seen. In the latter it is mostly in the chronic form. At younger ages deficiency diseases are likely to be less prevalent and mostly in the mild acute or beginning chronic state; at older ages they are apt to be more frequent and largely in the chronic form.

These influences are not invariable, absolute or completely decisive. Economic level and geographic region are far from perfect correlates of deficient diets, and age does not initiate a deficiency disease. Nor are these influences of equal weight. Perhaps the most influential is economic level. But many persons in the higher economic groups do have severe deficiencies, while some in the lower miraculously escape. Only a small proportion of persons in an endemic region

come down with a severe acute deficiency disease; almost all of these are in the low income group. As for the influence of age, adults may be normal, whereas children, particularly if they are from low income families, may exhibit a chronic process. We have seen numerous children from 8 to 11 years old and in low economic groups with chronic changes similar to those most frequent in the middle age group.

It is apparent that there is much malnutrition, most of it chronic in character. If we wish to be coldly scientific we can join the skeptic in asking: What of it? What is the justification for the expense and work in examining persons and treating the marginally malnourished? It is appropriate to raise the question whether the mild and chronic forms of malnutrition have any significance. Increasing evidence indicates that they have immediate and that they may also be found to have long range effects.

For one thing, troublesome symptoms occurring in these mild and chronic forms of malnutrition and their disappearance under treatment may be noted objectively. In ariboflavinosis, photophobia and lacrimation are frequently noted during the biomicroscopic examination.⁵⁶ Psychic manifestations have been observed in mild athiaminosis.¹⁴⁴ Doubtless, disturbing symptoms will be found in the mild stages of other deficiency diseases. Some are real handicaps. How much these symptoms dull the edge of health and lower performance in daily activities can now only be conjectured. In many instances, only after the symptoms have disappeared is their previous presence appreciated. Relief from such symptoms is no small benefit. The extent to which improvement is reflected in such activities as work remains to be demonstrated. In any event, relief from symptoms may be regarded as one justification for the diagnosis and specific treatment of these mild and chronic states.

INFLUENCE ON MORBIDITY

Moreover, there are many strong intimations, short of proof, that malnutrition has a contributory or determining role in the occurrence of other diseases. This is the much debated question of the influence of nutri-

144. Williams, R. D.; Mason, H. L.; Wilder, R. M., and Smith, B. F.: Observations on Induced Thiamine (Vitamin B₁) Deficiency in Man, *Arch. Int. Med.* **66**: 785-799 (Oct.) 1940.

tional status on morbidity. Up to now the lack of methods has made it difficult to supplant debate by demonstration on whether, or to what extent, impaired nutrition may play a part as a predisposing factor in parasitic diseases, such as tuberculosis, and whether satisfactory nutrition may aid in building up natural resistance against such diseases. With the present availability of methods, this very promising and hopeful vista may be explored. However, we must not look for too much from nutrition; we must not expect it to confer absolute protection against disease. Other circumstances, of course, exert their influence. Rather, let us say that nutrition at most may be one factor affecting the probability of disease occurring. If that should be demonstrated it would be sufficiently important to warrant evaluation of nutritional status as a routine procedure.

CHAPTER XXIII

NUTRITION IN PREVENTIVE MEDICINE

W. H. SEBRELL, M.D.

BETHESDA, MD.

The prevention of malnutrition and the deficiency diseases is probably the greatest and most complex problem in public health that this country has ever had. The exact extent of physical disability, economic loss and disease directly or indirectly related to nutrition are unknown, and yet there is every indication that malnutrition is very widespread. Some physicians who do not see many cases of advanced deficiency disease feel that the importance of nutrition is being overemphasized. However, in every clinic in which close observations are made and the more refined methods of diagnosis used, many unsuspected cases of malnutrition are recognized, and every study reveals the importance of mild degrees of deficiency in producing symptoms the cause of which was hitherto unrecognized. Furthermore, it is significant that almost all practicing physicians are prescribing vitamin preparations for more and more of their patients.

Even before our food supply was disturbed by the conditions incident to war, a number of surveys had all shown that a large part of our population was eating foods which failed to provide the essentials in amounts recommended for optimum nutrition. For example, a survey of the diets of more than a thousand workers in a large aircraft factory¹ revealed that more than four fifths of the diets studied fell below the amounts of certain nutrients recommended by the Food and Nutrition Board of the National Research Council.² Nutritionists who have watched workers select their lunches in cafeteria lines report that not more than half of them choose good lunches even when foods needed to provide good lunches are on the counters. It was also observed that women usually made poorer choices than men. The method of food preparation

1. Wiehl, Dorothy G.: Diets of a Group of Aircraft Workers in Southern California, *Milbank Mem. Fund Quart.* 20: 329, 1942.

2. Recommended Dietary Allowances, National Research Council, Reprint and Circular Series No. 115, January 1943.

also greatly affects its food value. In a study of food as it was served³ it was shown that as much as 90 per cent of the thiamine (B_1) present in the fresh raw food was lost before the food was eaten. Keeping food hot for long periods of time is really overcooking it, and the vitamins destroyed by heat and oxidation are thus lost. The hot lunch prepared and kept hot for hours before consumption may not be as satisfactory nutritionally as a cold one.

The effect of such inadequate diets on the ability of the civilian worker to do his part in the war effort must be of serious concern to us at this time. As a nation we are not as well fed as we once believed. Physicians and health officers must recognize that here is a whole new sphere of responsibility in the field of preventive medicine as great as or greater than the field of sanitation or control of communicable diseases.

The growing recognition of the importance of nutrition in health has gone hand in hand with the development of the science of nutrition. Most of what may be called the modern knowledge of nutrition has developed during the present century and much of it since World War I. The discovery of new vitamins, the recognition of the great physiologic importance of various mineral salts and better methods of diagnosis have made the entire world increasingly aware of the enormous amount of ill health, poor development, disease and disability due either directly or indirectly to malnutrition. An indication of the extent of the problem is given just by a survey of the fragmentary reports in the medical literature on the prevalence of the vitamin deficiency diseases.

The principal dietary deficiency diseases are nutritional edema, vitamin A deficiency, vitamin D deficiency, vitamin B_1 (thiamine) deficiency, nicotinic acid deficiency (pellagra), riboflavin deficiency (ariboflavinosis), vitamin C deficiency (scurvy) and vitamin K deficiency. These diseases occur to some extent throughout the world, although there are frequently wide variations in geographic distribution.

Although reports in many instances indicate an extensive occurrence of deficiency disease, they most probably represent only a small proportion of the cases actually occurring in the world.

3. Goodhart, Robert: Dietary Conditions in Industry, J. A. M. A. 121:93 (Jan. 9) 1943.

NUTRITIONAL EDEMA

Nutritional edema is an invariable accompaniment of famine and rapidly disappears when the patient is given enough food of good quality. Together with the prolonged undernutrition a deficiency of protein appears to be the most important factor in the production of this syndrome, although it is recognized that strenuous exercise, exposure to cold and probably other influences are contributory.

In mild cases the edema may be confined to the lower limbs, but when it is more severe it extends to all parts of the body. It is accompanied by emaciation, muscular weakness, depression, anemia and very frequently gastrointestinal disturbances. The swollen extremities are cold and painful when touched, the pulse is slow and the blood pressure is low.

This disease is very common in prison camps and during periods of famine. It has been especially prevalent in India and in China. During the latter years of the first world war it reached epidemic proportions among the poorer classes of the civilian populations of the central European countries. In Bohemia alone 22,842 cases were listed. In the Russian famine of 1921-1922 every single surviving inhabitant of certain towns was affected. During the present nutritional crisis in Europe and in China we may be certain that the incidence of nutritional edema is extremely high although no accurate figures are as yet available.

VITAMIN A

Vitamin A deficiency is manifested in human beings by lesions found chiefly in the epithelial structures. The most readily recognized symptoms are those of the severe deficiency states. Xerophthalmia is associated with atrophy of the paraocular glands, hyperkeratosis of the conjunctiva and finally involvement of the cornea leading to softening or keratomalacia and blindness. Nyctalopia, or night blindness, is due to a functional failure of the retina in the proper regeneration of visual purple. The characteristic skin lesions were first recognized in Chinese soldiers in 1931.⁴ The lesions consist of epidermal hyperplasia and glandular atrophy and are represented by papular eruptions around the

4. Frazier, C. N., and Hu, Ch'uan-K'uei: Cutaneous Lesions Associated with a Deficiency in Vitamin A in Man, *Arch. Int. Med.* **48**: 507 (Sept.) 1931.

pilosebaceous follicles. Unlike the ocular manifestations, cutaneous eruptions occur in persons between 16 and 30 years of age and not in infants. It is common among men, and 90 per cent of those showing the dermatosis have obvious ocular manifestations of vitamin A deficiency.⁵

The symptoms of milder deficiency states are more difficult to detect. Early stages of conjunctival xerosis occur which may be discovered only by biomicroscopic examination.⁶ Incipient night blindness may be demonstrable only by careful studies of dark adaptation for which a variety of photometric instruments and technics have been introduced. Mild dermatoses resembling the more florid eruptions of advanced vitamin A deficiency and responding to treatment with vitamin A preparations have been described.⁷ Levels of carotene and vitamin A in the blood and tissues have been determined in an effort to use them as criteria of deficiency states, either manifest or subclinical. Vitamin A has also been given a role in disorders of the respiratory tract,⁸ genitourinary tract,⁹ central nervous system,¹⁰ teeth,¹¹ thyroid gland¹² and other organ systems and structures.

Xerophthalmia and nyctalopia have been reported from almost every part of the world. In most countries it is infrequent except under unusual circumstances. It is prevalent, however, in India,¹³ China,¹⁴ the Dutch East Indies,¹⁵ other Asiatic areas,¹⁶ British Guiana¹⁷

5. Frazier, C. N., and Hu, Ch'uan-K'uei: Nature and Distribution According to Age of Cutaneous Manifestations of Vitamin A Deficiency, *Arch. Dermat. & Syph.* **33**: 825 (May) 1936.

6. Wiehl, Dorothy G., and Kruse, H. D.: *Milbank Mem. Fund Quart.* **19**: 241, 1941.

7. Youmans, J. B.: The Present Status of Vitamin Deficiencies in Practice, *J. A. M. A.* **108**: 15, (Jan. 2) 1937.

8. Blackfan, K. D., and Wolbach, S. B.: *J. Pediat.* **3**: 679, 1933. Shibley, G. S., and Spies, T. D.: The Effect of Vitamin A on the Common Cold, *J. A. M. A.* **103**: 2021 (Dec. 29) 1934. Cameron, H. C.: *J. Am. Dietet. A.* **11**: 189, 1935.

9. Higgins, C. C.: Production and Solution of Urinary Calculi, *J. A. M. A.* **104**: 1296 (April 13) 1935.

10. Mellanby, Edward: *Brain* **58**: 141, 1935.

11. Mellanby, May: *Physiol. Rev.* **8**: 545, 1928. Bessey, O. H., and Wolbach, S. B.: Vitamin A, *J. A. M. A.* **110**: 2072 (June 18) 1938.

12. Wendt, H.: *München med. Wchnschr.* **82**: 1679, 1935.

13. Kirwan, E. O.; Sen, K., and Biswas, R. B.: *Indian J. M. Research* **20**: 119 (Jan.) 1941. Eddy and Dalldorf⁴⁸ and references given in footnotes 19, 20 and 21.

14. References given in footnotes 13, 21 and 28.

15. Hadikoosomo, G. A.: *Geneesk. tijdschr. v. Nederl.-Indië* **78**: 935 (April 19) 1938. Ceylon Sessional Papers II, February 1927, and references given in footnotes 22, 23, 24, 25, 26, 28, 49 and 62.

16. *J. Malaya Branch Brit. M. A.* **3**: 113, 1938. Tupas, A. V., and Pecache, L.: *J. Philippine Islands M. A.* **18**: 147 (March) 1938, and references given in footnotes 27 and 28.

17. Report Director Medical Sources of British Guiana, 1938 (1940) p. 61.

TABLE 1.—*Reports of Occurrence of Nutritional Edema*

Area	Year	Incidence or Number of Cases Reported	Comment	References
United States (South).....	1942	15% of hospital patients		The Food and Nutrition of Industrial Workers in War-time, Nat. Res. Council Reprint and Circular Series No. 110, April 1942 Youmans: Am. J. Pub. Health 31: 704, 1941
United States (Tennessee)...	1941	Relatively small number	900 people studied; 30% of adults had hypoproteinemia	Dodd and Minot: J. Pediat. 8: 442, 1936 McLester: J. A. M. A. 106: 1865, 1936
United States.....	1936	41 cases.....	9 years' observation.....	
United States.....	1936	Not now common.....	Possibly increased during first years of depression	
India (Rangoon).....	1934	Increasing.....	With increasing trade depression	Kundu: Indian M. Gaz. 69: 439, 1934
China.....	1943	130 children, 14%.....	Of 903 patients admitted to hospital	Chen: Am. J. Dis. Child. 63: 553, 1942
China (Manchuria).....	1937	21 cases.....	Of 270 persons.....	Dol: J. Orient. Med. 27: 115, 1937
Spain.....	1943	12%.....		Robinson, Janney and Grande: J. Nutrition 24: 557, 1943
Spain.....	1940	One of 5 main deficiency diseases	3,116 people studied; 64% of women and 36% of men had a deficiency disease	Jimenez Garcia and Grande Oovian: Rev. clin. espafola 1: 41, 313, 318, 323, 1940
Netherland East Indies.....	1940	Cases reported.....	Due to failure of harvests of 1937 and 1938	Streef, Streef Spann and Ismangil: Geneesk. tijdschr. v. Nederlandisch-Indië 90: 990, 1940
East Africa (Kenya).....	1938	12 cases.....	April to October, 1937....	Bell: East African M. J. 14: 327, 1938
Egypt.....	1938	18 infants.....		Shukry, Mahdi and El Gholmy: Arch. Dis. Childhood 13: 254, 1938
Uganda.....	1939	Considerable in prisons up to about 1934		
Northern Rhodesia.....	1939	Reported.....		
British Honduras.....	1939	Reported.....		
Fiji.....	1939	Reported.....		
Sierra Leone.....	1939	Extensive in prisons, barracks and asylums		
Bechuanaland.....	1939	Frequent.....		
Leeward Islands (Antigua)...	Not uncommon.....		

Report of Committee on Nutrition for British Colonial Empire, 1939

and sections of Africa.¹⁸ A study in South India¹⁹ in 1937 found as many as 15 per cent of 4,000 school children showing xerophthalmia and keratomalacia. In Bengal²⁰ xerophthalmia and nyctalopia were found in 9 per cent of 2,000 persons. In Tientsin, China,²¹ a survey of school children uncovered the presence of xerophthalmia in 83 per cent of certain groups. Five per cent of children admitted to a Batavia hospital²² were xerophthalmic, and in Groot-Atjeh²³ it was found to be "widespread." In Ceylon²⁴ 65 per cent of the blindness was attributable to xerophthalmia, the latter being noted as "common." Of 500,000 persons in Java²⁵ about 1 per cent of blindness was found, and here too xerophthalmia was the chief cause. In Sumatra²⁶ 20 to 61 per cent of 3,684 children showed evidences of xerophthalmia, and in 1939 1 per cent of 8,677 children examined in the Philippine Islands²⁷ had this disease. In 1937 keratomalacia, xerophthalmia and nyctalopia were reported as "common" in the British Solomon Islands,²⁸ as "unknown" in the New Hebrides Condominium,²⁸ as "existing" in the Tonga Islands²⁸ and "almost completely absent" in the Fiji Islands.²⁸

Reports²⁹ from Tanganyika Territory in 1939 showed 10 per cent of the school boys to be suffering from night blindness. In Teso, Uganda,⁴⁰ a 30 per cent incidence of xerophthalmia was found among children in a group of 1,112 persons of all ages. In Cairo, Egypt,³¹ only 0.2 per cent of persons attending a general ophthalmologic hospital were nyctalopic, and 0.4 per cent

18. McKenzie.²⁰ Loewenthal.³⁰

19. League of Nations Report on Health Organization in British India, Geneva, 1937, p. 51.

20. Biswas, R. B.: Indian M. Gaz. **76**: 747 (Dec.) 1941.

21. Nicholls, L.: Indian M. Gaz. **68**: 681 (Dec.) 1933; **69**: 241 (May) 1934.

22. DeHaas and others: Geneesk. tijdschr. v. Nederl.-Indië **80**: 928, 1940.

23. Gomperts, C. E.: Geneesk. tijdschr. v. Nederl.-Indië. **80**: 1192 (May 7) 1940.

24. League of Nations Health Organization Reports, Geneva, 1937.

25. Tijssen, J.: Geneesk. tijdschr. v. Nederl.-Indië **79**: 79 (Jan. 10) 1939.

26. Maas: Geneesk. tijdschr. v. Nederl.-Indië **79**: 1512 (June 13) 1939.

27. Ubaldo, A. R., and de Campo, G.: J. Philippine Islands M. A. **19**: 483 (Aug.) 1939.

28. League of Nations Health Organ., Intergov. Conference of Far Eastern Countries on Rural Hygiene, Geneva, 1937.

29. McKenzie, A.: Tr. Roy. Soc. Trop. Med. & Hyg. **32**: 717 (April) 1939.

30. Loewenthal, L. J. A.: J. Trop. Med. & Parasitol. **29**: 349, 1935.

31. 8th Annual Report of the Giza Memorial Ophthalmic Lab., 1938, p. 105.

showed xerosis of the conjunctiva and cornea. No cases were found in a thorough 1942 survey of 841 children in the Union of South Africa³² and none were noted in the Falkland Islands.³³

In Europe, xerophthalmia is uncommon.³⁴ Up to 1939 only 7 cases had been reported in the French medical literature,³⁵ and reports up to 1941³⁶ failed to add any further cases. Under unusual circumstances the disease appeared in epidemic form, as in Denmark³⁷ during World War I, when dairy products were replaced in the diet by fats lacking in vitamin A. A recent survey of 106 families including 561 persons in Madrid, Spain,³⁸ uncovered only 2 per cent with nyctalopia. In Italy, however, the incidence is reported to be much higher. In Turin in 1939³⁹ 45 per cent of 500 school children had night blindness, and it was also found to be common in Venice.⁴⁰ A study of rural populations⁴¹ revealed that nyctalopia and dermatosis were "frequently reported" from Sweden, Norway, Finland, Czechoslovakia and Yugoslavia. A year earlier, in 1938, a report⁴² from Prague based on a questionnaire survey found no serious deficiencies, although dermatoses and nyctalopia were noted. In Halle, Germany,⁴³ in 1939 17 per cent of 218 persons were found to be night blind.

In the United States⁴⁴ xerophthalmia, keratomalacia and nyctalopia due to vitamin A deficiency are rarities.

32. Brock, J. F., and Latky, J. M.: *South African M. J.* **16**:255 (July 11) 1942.

33. Annual M. & Saint. Report, 1937, p. 24.

34. Brewis and others: *Ann. Rep. M. O. H. City & County of Newcastle upon Tyne for 1939*, appendix A, p. 12. Chevallier, A.: *Bull. Soc. sc. hyg. aliment.* **28**:61, 1940. Minoli, R. F.: *Milbank Mem. F. Quart.* **20**:213, 1942. Mowinkel, Reistrup and Reiter,³⁵ and the references given in footnotes 38, 39, 40, 41, 42, 43, 47, 53, 56, 57, 59 and 60.

35. Clement, R., and Delon, J.: *Arch. de méd. d. enf.* **42**:698 (Nov.-Dec.) 1939.

36. Youmans, J. B.: *J. Am. Dietet. A.* **18**:87 (Feb.) 1942.

37. Widmark, E.: *Lancet* **1**:1206, 1924.

38. Robinson, W. D.; Janney, J. H., and Grande Covian, F.: *J. Nutrition* **24**:557 (Dec.) 1942.

39. Mathis, G.: *Gior. d. r. Accad. d. med. d. Torino* **102**:218 (July-Sept.) 1939.

40. Bretti and Tria: *Ric. sc. prog. & C.* **10**:1107, 1939. Tria: *Quad. nutrizione* **6**:319, 1939.

41. *Bull. Health Organ. League of Nations* **8**:470, 1939.

42. Charvat: *Bull. Office. internat. hyg. pub.* **30**:591, 1938.

43. von Drigalski and others: *Klin. Wehnschr.* **18**:875, 1939.

44. Schnedorf, J. G.; Weber, C. J., and Clendening, Logan: *Am. J. Digest. Dis.* **9**:188 (June) 1942. Krupp, M. A.: *The Incidence of Nutritional and Vitamin Deficiency*, *J. A. M. A.* **110**:1475 (Aug. 29) 1942. Youmans, J. B., and Patton, E. W.: *Nutritional Deficiencies*, Philadelphia, J. B. Lippincott Company, 1941. Milam, D. F.: *Am. J. Pub. Health.* **32**:406 (April) 1942. Widmark.³⁷ Lewis and Haig.⁵⁴

TABLE 2.—*Reports of Occurrence of Vitamin A Deficiency*

Country and Year	Deficiency Symptom	Incidence	Groups Studied	References
NORTH AND SOUTH AMERICA				
Newfoundland, Labrador..... 1939-1940	Xerophthalmia, 0%; dark adaptation, 9%; nyctalopia, 8%	"Probably more extensive use of controlled procedures will show that even very mild vitamin A deficiency ordi- narily is rare in occidental population." Evidence of vitamin A def- iciency None	853 adults	Steven and Wald ⁴⁴
Canada (Edmonton)..... 1939	Dark adaptation, 24%		1,000 university students	Pett ²³
United States (Kansas)..... 1943	Clinical evidence	None	1,295 workmen	Schnedorf, Weber and Glendening ⁴⁴
United States (Chicago)..... 1943	Dark adaptation, blood levels	"Mild deficiency is rare or not detectable by these methods." 86.6% showed evidence of vitamin A deficiency	Children	Oldham, Roberts, MacLennan and Schultz ²³
United States (New York City).. 1941	Biomicroscopic, slit lamp examination	None	Poor school children	Wiehl and Kruse ²
United States (California)..... to 1945	Clinical deficiencies		385 hospital patients	Krupp ⁴⁴
United States (general)..... to 1941	Xerophthalmia	One case in several years re- ported in literature	Younans and Patton ⁴⁴
United States (general)..... to 1943	Nyctalopia, derma- tosis, anatomic changes, "mild deficiency," clinical deficiencies	"Not uncommon"	Younans and Patton ⁴⁴
United States (North Carolina). 1940-1941	Blood level at lower limits	None	Mill village com- munity of 400	Milam ⁴⁴
United States (Tennessee)..... 1941	Dark adaptation	"Common"	900 rural people	Younans, footnote 52, first reference
United States (Florida)..... 1941	Follicular conjunc- tivitis	"High incidence" of vitamin A deficiency	1,041 school children	Sandels, Cate, Wilkinson and Graves ²³
United States (New York City).. 1940	Dark adaptation	21.7% had vitamin A def- iciency One case	144 children	Lewis and Haig ⁴⁴
United States (Tennessee)..... 1938	Dark adaptation	50% showed vitamin A deficiency	54 adults in Nashville	Corlette, Youmans, Frank and Cor- lette ²³
United States..... to 1937	Dark adaptation	35% showed vitamin A deficiency	Medical students	Jeghers ²³
United States..... to 1937	Dark adaptation	50% showed vitamin A deficiency	Children patients	Younans, footnote 52, second reference
United States (Iowa)..... to 1936	Dark adaptation	26 to 79% showed vitamin A deficiency	Children	Jeanes, Blanchard and Satterthwaite ⁴⁴
Brazil..... 1933-1935	Nyctalopia	"A number of cases were ob- served during a period of drought"	General popu- lation	Cavalcanti ⁴⁷

British Guiana.....	1933	Xerophthalmia, nyctalopia	"Common"	Footnote 17
Yucatan and Labrador.....	to 1937	Xerophthalmia, nyctalopia	"Common"	General popu-lation	Eddy and Daldorf ⁴⁵
United States (general).....	to 1934	Xerophthalmia	"Rare"	Thorson: J. A. M. A. 1933: 1438 (Nov. 10) 1934
Trinidad.....	1941	Xerophthalmia, nyctalopia	"Rare"	Metivier ⁴⁸
EUROPE					
England.....	1940	Hyperkeratosis	5% had this evidence of vitamin A deficiency	General popu-lation	Pemberton ⁵⁰
England (Newcastle upon Tyne)	1938-1939	Clinical deficiencies	None	138 (poor in- come group) children	Brewis and others ⁵⁴
France (Marseilles).....	1941	Clinical deficiencies: "Laboratory data indicating mild deficiencies"	None	Several hundred of school children and general population	Youmans ⁵⁶
France.....	1940	"Total deficiency, partial deficiency (Dry skin, digestive disturbance, nyctalopia, irritability) Xerophthalmia	Widespread	Adults and children	Chevallier ⁵⁴
France.....	to 1939	Xerophthalmia	Rare
France (Paris)	1940-1941	Dark adaptation	Prevalent	General litera- ture	Clement and Delon ⁵⁵
France.....	1938	Nyctalopia, 9%: dermatosis, 15%: blood level at or below borderline 35% Nyctalopia	Only 7 cases described to date	In hospitals	Minoll ⁵⁴
Spain (Madrid).....	1941	Nyctalopia, 9%: dermatosis, 15%: blood level at or below borderline 35% Nyctalopia	Same as before (?)	210 school children	Caussade and others ⁵⁷
Italy (Turin).....	1939	Nyctalopia, 9%: dermatosis, 15%: blood level at or below borderline 35% Nyctalopia	"Relatively frequently"	103 families or 561 persons	Robinson, Janney and Grande Covian ⁵⁸
Italy (Venice).....	1939	Nyctalopia, 9%: dermatosis, 15%: blood level at or below borderline 35% Nyctalopia	Evidences of vitamin A deficiency	500 school children	Mathis ⁵⁹
Italy (Venice).....	1939	Nyctalopia, 9%: dermatosis, 15%: blood level at or below borderline 35% Nyctalopia	45% showed this vitamin A deficiency	Bretti and Tris ⁴⁰
Italy (Venice).....	1939	Nyctalopia, 9%: dermatosis, 15%: blood level at or below borderline 35% Nyctalopia	Frequent incidence of these vitamin A deficiencies	Children	Tris ⁴⁰
Czechoslovakia (Prague).....	1938	Nyctalopia, 9%: dermatosis, 15%: blood level at or below borderline 35% Nyctalopia	"Common" occurrence of this vitamin A deficiency	Replies to 1,218 questionnaires sent to health officers	Charvat ⁴⁴
Sweden (Djuroholm).....	1939	Nyctalopia, 9%: dermatosis, 15%: blood level at or below borderline 35% Nyctalopia	"No serious deficiency (vitamin A) but a slight lack of the vitamin was indicated by dry affection of the skin and nyctalopia."	67 school children	Abramson and Orgaard ⁵⁸
Finland (Helsinki).....	1940	Nyctalopia, 9%: dermatosis, 15%: blood level at or below borderline 35% Nyctalopia	22% showed this vitamin A deficiency	71 persons	Nylund ⁵⁹
Finland (Helsinki).....	1940	Nyctalopia, 9%: dermatosis, 15%: blood level at or below borderline 35% Nyctalopia	22% showed this vitamin A deficiency

TABLE 2.—*Reports of Occurrence of Vitamin A Deficiency—Continued*

Country and Year	Deficiency Symptom	Incidence EUROPE—Continued	Groups Studied	References
Finland (Helsinki)..... 1938-1940	Dark adaptation	16.2% showed this vitamin A deficiency	1,377 persons	Simola and Saksela ³⁹
Denmark (Copenhagen)..... 1937	Dark adaptation	2.4% "uncommon"	332 hospital patients	Mowinkel-Reistrup and Reiter ²³
Denmark (Copenhagen)..... 1935	Dark adaptation	71% showed this vitamin A deficiency	65 children	Frandsen ²⁶
Germany (Posen)..... 1942	Dark adaptation	None	173 persons	Widenbauer ⁶⁰
Germany (Halle)..... 1939	Nyctalopia	17% showed this vitamin A deficiency	218 persons	von Drigalski and others ⁴³
Sweden, Norway, Finland, Czechoslovakia, Yugoslavia, 1939	Nyctalopia, dermatosis	"Frequently reported"	Rural population	Bull Health Organ. ⁴¹
Egypt (Cairo)..... 1938	Xerosis of conjunctiva and cornea, nyctalopia	0.4%	Patients in general ophthalmic hospital	Giza Memorial ²¹
Tanganyika Territory..... 1939	Dark adaptation, nyctalopia 10%	0.2% 93% showed this vitamin A deficiency	94 natives and convicts; school boys	McKenzie ²⁹
Uganda (Teso)..... 1935	Xerophthalmia, phrynoderma	300 cases, 30% in children, 8.7% in adults	1,112 persons	Loewenthal ³⁰
Union of South Africa..... 1942	Keratomalacia, Bitot's spots	None	841 children	Brock and Latsky ²²
Phrynoderma				
Xerophthalmia				
Falkland Islands..... 1937		"Considerable number"	Annual report ³³
ASIA				
India (Calcutta)..... 1941	Dark adaptation, nyctalopia	6% of these vitamin A deficiencies	138 persons	Roy and Bauergee ⁶¹
India (Calcutta)..... 1941	Lesions from nyctalopia to xerophthalmia	3%	14,698 persons in eye infirmary	Kirwan, Sen and Biswas ¹³
India (Bengal)..... 1941	Xerophthalmia, nyctalopia	9%	2,000 persons	Biswas ²⁰
India (Bengal)..... 1941	Dark adaptation	"27% were below standard"	391 school boys	Basu and De ⁶¹
India (general)..... to 1937	Xerophthalmia, nyctalopia	"Common"	General population	Eddy and Daldorf ⁴⁵
India (Kashmir)..... 1939	Phrynoderma	10% showed this vitamin A deficiency	Children	Nicholls and Nimalasuriya ⁴⁹
South India..... 1937	Xerophthalmia, keratomalacia	Up to 15%	4,000 school children	League of Nations ¹⁹

China.....	Xerophthalmia, nyctalopia	"Common"	General popu- lation	Eddy and Dalldorf ⁴³
to 1937	Xerophthalmia	Eye clinic patients 6%, charity boarding schools 83%, poor vernacular schools 29%, upper class schools 3%, mental asylums 44%, mental asylums (Europe), 2% "Not uncommon"	Nicholls ²¹
1928-1930	Xerophthalmia	5%	Children	Malaya Journal ¹⁶
Malaya (Singapore).....	Xerophthalmia	"Wid-spread"	Children ad- mitted to hospital	De Haas and others ²²
1938	Xerophthalmia	60 to 80% showed this vita- min A deficiency	Gomperts ²³
Dutch East Indies (Batavia) ...	Xerophthalmia	1.3%	480 persons	Gorter ⁴²
1935-1940	Xerophthalmia	"Common"	3,000 children under 15 years	Hadikoesomo ¹⁵
Dutch East Indies (Groot-Atjeh)	Dark adaptation	"Common"	League of Nations Conference ²⁴
1937	Dutch East Indies (Batavia)....	"Common"	
1937-1939	Xerophthalmia	"Common"	
1938	Xerophthalmia, keratomalacia, nyctalopia	"Common"	
1938	Xerophthalmia, keratomalacia	"Common"	
1937	As above	"Common"	
China.....	As above	"Unknown"	
1937	As above	"Exists"	
British Solomon Islands.....	As above	"Almost complete absence"	
1937	As above	About 1% blindness, of which xerophthalmia is chief cause	500,000 persons	
New Hebrides (Condominium)...	As above	39% to 2 years; 51-61%, 2-15 years; 20%, 15 years	3,684 children	Maas ²⁶
1937	As above	21%, 5.6%	978 children	Nicholls and Nimalasuriya ⁴⁵
Tonga Islands.....	As above	Less than above	1,497 children	Nicholls and Nimalasuriya ⁴⁵
1937	As above	65% of blindness caused by xerophthalmia	League of Nations ²⁴
Fiji Islands.....	As above	"Common"	Prisoners	Ceylon Sessional Papers ¹⁵
1937	Xerophthalmia	1%	8,677 persons	Ubaldo and de Campo ²⁷
Dutch East Indies (W. Java)....	Xerophthalmia	47 cases noted	Pediatric service of General Hospital in children—5 yrs.	Tupas and Pecache ¹⁶
1939	Xerophthalmia (mild and severe)			
Dutch East Indies (Sumatra)...	Xerophthalmia			
1939	Xerophthalmia			
Ceylon (Southern).....	Xerophthalmia			
1939	Xerophthalmia			
Ceylon (Northern).....	Xerophthalmia			
1937	Xerophthalmia			
Ceylon.....	Xerophthalmia			
1937	Xerophthalmia			
Philippine Islands.....	Xerophthalmia			
1939	Xerophthalmia			
Philippine Islands.....	Xerophthalmia			
1927-1937	Xerophthalmia			

In Yucatan⁴⁵ and British Guiana¹⁷ they are reported as "common." A recent study in Newfoundland and Labrador⁴⁶ uncovered no cases of xerophthalmia and only 3 per cent of night blindness among 353 adults. In Brazil⁴⁷ a number of cases of nyctalopia were noted during a period of drought. The conditions were reported from Trinidad⁴⁸ as of "rare" occurrence.

The severe dermatoses of vitamin A deficiency are found in the same geographic distribution as the advanced ocular manifestations. Reports from China⁵ and other countries⁴⁹ indicate the incidence of this symptom to be as high as or higher than that of ocular symptoms. The occurrence of mild dermatoses as evidence of low grade vitamin A deficiency has been reported widely. Five per cent of a general population group in England⁵⁰ in 1940 showed such a hyperkeratosis, and 13 per cent of a similar group in Madrid, Spain,³⁸ in 1941 had such lesions. It has been frequently reported from the Scandinavian countries,⁴¹ central Europe,⁵¹ Asia⁴⁹ and South Africa.⁵²

The failure of the eye to adapt properly to darkness has been reported as a mild vitamin A deficiency symptom and has been subjected to refined biophotometric measurement. Reports of such studies have been at variance as the result of the multitude of technics and instruments employed, the failure to consider other etiologic factors of dysadaptation and the unavailability of universally accepted criteria of subclinical vitamin A deficiency disease to serve as standards.

A high incidence of dark dysadaptation has been reported widely in the United States⁵² and throughout the world.⁵³ Among 120 Iowa school children⁵⁴ almost 20 per cent showed abnormal adaptation in the winter

45. Eddy, Walter and Dalldorf, Gilbert: *The Avitaminoses*, Baltimore, Williams and Wilkins, 1937.

46. Steven, D., and Wald, G.: *J. Nutrition* **21**: 461 (May) 1941.

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50. Pemberton, J.: *Lancet* **1**: 871 (May 11) 1940.

51. Charvat.⁴² *Bull. Health Organ.*⁴²

52. Youmans, J. B.: *Am. J. Pub. Health* **31**: 704 (July) 1941; *The Present Status of Vitamin Deficiencies in Practice*, J. A. M. A. **108**: 15 (Jan. 2) 1937. Jeghers, Harold: *The Degree and Prevalence of Vitamin A Deficiency in Adults*, *ibid.* **109**: 756 (Sept. 4) 1937. Corlette, Youmans, Frank and Corlette.⁴³ *Jeans and Zentmire.*⁴⁴

53. Pett, L. B.: *J. Biol. Chem.* **128**: lxxviii (June) 1939. Mowinkel, E.; Reistrup, H. H., and Reiter, P. J.: *Hospitalstid.* **80**: 989 (Sept. 7) 1937. Baau and De⁴⁵ and the references given in footnotes 29, 43, 46, 56, 57, 58, 59, 60, 61 and 62.

54. Jeans, P. C.; Blanchard, Evelyn L., and Satterthwaite, Franklin E.: *Dark Adaptation and Vitamin A*, *J. Pediat.* **18**: 170 (Feb.) 1941.

and 5 per cent in the fall. Of 54 adults studied in Tennessee⁵⁵ 27 had subnormal abilities to adapt to darkness. In Copenhagen⁵⁶ 46 of 65 healthy school children showed this impairment. Similar findings have been reported from France,⁵⁷ Sweden,⁵⁸ Finland,⁵⁹ Germany,⁶⁰ India,⁶¹ Africa²⁰ and the Dutch East Indies.⁶² However, reports indicating a very low incidence of dark dysadaptation are also available. A study of Chicago children⁶³ in 1942, augmented by determinations of vitamin A blood levels, led to the conclusion that "mild vitamin A deficiency is rare or not detectable by these methods." Only 1 case of dark dysadaptation⁶⁴ was found among 144 New York City school children.

Very mild degrees of conjunctival xerosis recently have been attributed to a deficiency of vitamin A. By means of a bimicroscopic slit lamp, 86.6 per cent⁶ of poor school children in New York City were found to exhibit such lesions. A follicular conjunctivitis also thought to be etiologically related to vitamin A deficiency was present in 21.7 per cent of 1,041 Florida⁶⁵ school children.

VITAMIN D DEFICIENCY

Nutritional diseases due to deficiencies of vitamin D and calcium may be divided into three important categories, namely rickets, osteomalacia and tetany. The three conditions, though usually separated for descriptive purposes, have ramifications that make it difficult to separate them completely.

Rickets.—Neff⁶⁶ defines rickets as a "nutritional and metabolic disease of the first two years of life, the chief

55. Corlette, M. B.; Youmans, J. B.; Frank, Helen, and Corlette, Mildred G.: *Am. J. M. Sc.* **195**: 54 (Jan.) 1938.

56. Frandsen, H.: *Nutrition Abstr.* **4**: 621, 1935.

57. Caussade, L., and others: *Rev. franc. pediat.* **14**: 209, 1938.

58. Abramson and Ørgaard: *Skand. arch. f. physiol.* **82**: 49, 1939.

59. Nylund, C. E.: *Nord. med. (Finska läk.-sällsk. handl.)* **9**: 659 (March 1) 1941. Simola, P. E., and Saksela, N., *ibid.* **9**: 275 (Jan. 25) 1941.

60. Widenbauer, F.: *Ernährung* **7**: 97, 1942. von Drigalski and others.⁶

61. Roy and Bauergee: *Ann. Biochem. Exper. Med.* **1**: 127, 1941. Basu, N. M., and De, N. K.: *Indian J. M. Research* **29**: 591 (July) 1941.

62. Gorter, F. J.: *Geneesk. tijdschr. v. Nederl.-Indië* **79**: 1181, 1939.

63. Oldham, Helen; Roberts, Lydia J.; MacLennan, Kathryn, and Schlutz, F. W.: *J. Pediat.* **90**: 740 (June) 1942.

64. Lewis, J. M., and Haig, C.: *J. Pediat.* **16**: 285 (March) 1940.

65. Sandela, Margaret R.; Cate, Helen D.; Wilkinson, Kathleen P., and Graves, L. J.: *Follicular Conjunctivitis in School Children as an Expression of Vitamin A Deficiency*, *Amer. J. Dis. Child.* **69**: 101 (July) 1941.

66. Neff, Frank C.: *Rickets*, in *Tice's Practice of Medicine*, **9**, Sec. XIII, chapter VIII, Hagerstown, Md., W. F. Prior Company.

TABLE 3.—Occurrence of *Rickets*

Area Reported	Year	Number Examined	Number or Percentage of Cases Found		References
			Incidence of 75 to 97.6%		
Portland, Ore.....	1936	1,000	97.6%		
Hamburg, Germany.....	95 %		
Riga.....	86 %		
Boston.....	79 %		
Dresden, Germany.....	89 %		
Durham, England.....	1935	1,287 boys	81.8%		
Durham, England.....	1935	1,122 girls	76 %		
Land, Sweden.....	1934	141	108 or 76 %		
Portland, Ore., and San Diego, Calif.	1937	913	90 %		
Frankfurt, Germany.....	1939	599	80.8%		
Reich, Germany.....	Winter of 1940	...	75 %		
Germany.....	Winter of 1939	599	75 %		
Egypt.....	1935	Incidence of 25 to 74.9%		
Egypt.....	1938	240	50 %		
Lausanne, Switzerland.....	1937	438	104 or 43.3%		
Kings Lynn, England.....	1935	651 boys	271 or 61.3%		
Buenos Aires, Argentina.....	1932	1,000	29.1%		
Buenos Aires, Argentina.....	1934	408	356 or 35.6%		
Buenos Aires, Argentina.....	1939	186	32 %		
Nomed Laplanders.....	1939	140	36.8%		
Cantons of Colmar and Andolscheln..	1936	192	44 or 31.4%		
Baltimore.....	1943	230	45 %		
			46.5%		

Moore and Dennis ⁶⁹McIntosh ⁷¹Siwe ⁷⁰Moore and others ⁶⁷Graser ⁶⁸Rott ⁶⁸Graser ⁶⁸Sabri ⁷²Huidschinsky ⁷³Messerli ⁷³McIntosh ⁷¹Sujoy ⁷⁵Garrahan ⁷⁵Giordano ⁷⁵Gezellum ⁷⁶Zillhardt ⁷⁷Follis, Jackson, Eliot and Park ⁷⁴

Norway (inland).....	Not given	917	Under 1 yr. 30 % 1 to 3 yrs. 40 %	Rustung ⁷⁸
City of Freiberg, Germany.....	1936	1,431	47 %	Viethen ⁷⁹
Adjoining rural districts.....	1936	70 %	Hofmeier ⁷⁹
Sudetenland.....	1940	30 to 70 %	Rott ⁸⁸
Reich, Germany.....	Summer of 1940	50 %	Graser ⁸⁸
Germany.....	June and July 1941	412	42 %	Reichsgesundtbl. 14 : 343, 1942
Aussig, Germany.....	1938-1939	4,439	2,918 or 65.7%	
		Incidence of 0 to 24.9%		
Hong Kong, China.....	1939	None	Wellington ⁸⁰
Panama Canal Zone.....	1933	100	8 or 8 %	Elliot and Jackson ⁸¹
Puerto Rico.....	1933	564	5 or 0.9%	Gruenfelder ⁸²
Palestine.....	1937	950 sick children in hospitals	11 or 1.1%	Gruenfelder ⁸²
Palestine.....	1937	6,203 outpatients	57 or 0.9%	Carran and Bazzano ⁸³
Uruguay.....	1937	Children hospitalized in early infancy	15 to 12 %	Niosi ⁸⁴
Africa.....	1939	2,000	4 or 0.2%	Freyes ⁸⁵
France.....	1936	In schools in cities and villages	4 to 6 %	Armand, M.: Gaz méd. Paris 43 : 53, 1936
Haiti.....	1936	Relatively rare	Schwenk, E.: München. med. Wchnschr. 83 : 1395,
Swedish Laplanders.....	1936	Practically no rickets	1936
Hamburg, Germany.....	1929	908	101 or 15 1/2 %	Zell, W., ibid 84 : 1865, 1937
Hamburg, Germany.....	1936	1,245	21.3%	Petragnane ⁸⁶
Italy.....	1938	0.5 to 1.5%	Velasco ⁸⁷
Ecuador.....	1936	Rickets in exceptional cases	Armand ⁸⁸
Haiti.....	1936	Relatively rare	Ordonezdiaz ⁸⁹
Honduras.....	1936	Very rare	Suarez ⁹⁰
Peru.....	1933	32,000	0.18%	
Peru.....	1934	32,000	0.16%	

characteristic of which is a failure to appropriate or retain calcium in the bones, which become soft and deformed."

The existence of rickets has been demonstrated throughout most of the world, varying in its frequency and severity in various localities. The greatest local prevalences were found in larger cities where poor housing, inadequate diets and limited exposure to sunshine exists. The disease has been reported to be, as a rule, most prevalent in the north temperate zone and least prevalent in the tropical and subtropical areas.

An incidence of 75 to 97.6 per cent of children having symptoms of rickets has been reported in certain areas of the United States,⁶⁷ in Germany,⁶⁸ Italy,⁶⁹ Sweden,⁷⁰ the British Isles⁷¹ and Egypt,⁷² in from 25 to 75 per cent of children in Switzerland,⁷³ in the United States,⁷⁴ the British Isles⁷¹ and Argentina,⁷⁵ among nomad Laplanders,⁷⁶ in the cantons of Colmar and Andolsheim,⁷⁷ in Norway⁷⁸ and Germany⁷⁹ and from 0 to 25 per cent in localities in China,⁸⁰ the Panama Canal Zone,⁸¹ Puerto Rico,⁸¹ Palestine,⁸² Uruguay,⁸³ Africa,⁸⁴

67. Moore, C. U.; Brodie, Jessie L.; Thornton, A. J.; Lesem, A. M., and Cordua, Olive B.: Failure of Abundant Sunshine to Protect Against Rickets, *Am. J. Dis. Child.* **54**: 1227 (Dec.) 1937. Moore and Dennis.⁶⁹

68. Graser, E.: *Ztschr. f. Kinderh.* **61**: 520, 1939. Rott, H. J.: *Reichsgesdhl.*, 1940. Graser, E.: *Klin. Wchnschr.* **21**: 82, 1942. Moore and Dennis.⁶⁹

69. Moore, C. U., and Dennis, H. G.: *California & West. Med.* **44**: 288 (April) 1936.

70. Siwe, S.: *Acta pædiat.* **17**: 1, 157, 184, 1934.

71. McIntosh, J. W.: *J. State Med.* **43**: 187 (April) 1935.

72. Huldshinsky, K.: *Brit. J. Phys. Med.* **1**: 297 (Sept.) 1938. Sabri, S.: *J. Egyptian M. A.* **18**: 138 (Feb.) 1935.

73. Messerli, F. M.: *Rev. d'hyg.* **59**: 640, 1937.

74. Follis, R. H., Jr.; Jackson, Deborah; Elliot, Martha M., and Park, E. A.: Prevalence of Rickets in Children Between Two and Fourteen Years of Age, *Am. J. Dis. Child.* **66**: 1 (July) 1943.

75. Sujoy, E.: *Semana méd.* **40**: 646, 1933. Garrahan, J. P., and Muzio, E., *ibid.* **41**: 392, 1934. Giordano, J. J., *ibid.* **46**: 460, 1939.

76. Gezelium, G.: *Acta pædiat.* **26**: 184, 1939.

77. Zillhardt, A.: *Bull. Soc. pædiat., Paris* **34**: 373, 1936.

78. Rustung, E.: *Acta pædiat.*, 1935, **17**, supp. 2, p. 33.

79. Viethen, A.: *Arch. f. Kinderh.* **115**: 13, 1938. Hofmeier, K.: *ibid.* **120**: 49, 1940. Zell, W.: *München. med. Wchnschr.* **84**: 1895, 1937. Rott.⁶⁸ Graser.⁶⁸

80. Wellington, A. R.: *Hong Kong M. & San. Report for Year 1932*, p. 60.

81. Elliot, Martha M., and Jackson, Edith B.: Bone Development of Infants and Young Children in Puerto Rico, *Am. J. Dis. Child.* **46**: 1237 (Dec.) 1933.

82. Gruenfelder, B.: *M. Rec.* **146**: 176, 1937.

83. Carran, A., and Bazzano, H. C.: *Arch. pædiat. Uruguay* **8**: 428, 1937.

84. Niosi, A.: *Minerva Med.* **30**: 454, 1939.

France,⁸⁵ Italy,⁸⁶ Ecuador,⁸⁷ Haiti,⁸⁸ Honduras⁸⁹ and in Peru.⁹⁰

The disease in itself is rarely fatal, but intercurrent infections may develop that are difficult to control, owing to the low resistance of the individual. The Bureau of the Census⁹¹ for the United States lists rickets as a cause of death in each of nine years from 1933 through 1941 as ranging from 339 to 139. In England and Wales⁹² it was listed as the cause of death for eleven years from 1928 through 1938 as ranging from 493 to 124. There were 554 deaths in Italy in 1937,⁹³ 129 in Colombo, Ceylon, in 1939,⁹⁴ 21 deaths of 57 patients with rickets admitted to all hospitals in the Malaya States in 1938⁹⁵ and 170 deaths of 195 patients with rickets in hospitals in Chile in 1942.⁹⁶

Osteomalacia.—This is a nutritional disease of adults resulting from deficiency of vitamin D and the failure of utilization of calcium. It is characterized by pronounced softening of bones, so much so that they become flexible and cause deformities, especially of the limbs, spine, thorax and pelvis. It is attended by the rheumatic type of pain and general weakness. Although it is occasionally seen in men it is most often encountered in women, especially among those who are pregnant.

Although osteomalacia has become an exceptional disorder among peoples living under modern civilizations, there are still large areas where it constitutes a medical problem. It was reported to be widely distributed in India,⁹⁷ in the province of Shansi, China,⁹⁸ in the province of Toyama, Japan,⁹⁹ and in an isolated district of

85. Freyss, M. M.: Bull. Soc. pediat., Paris 34: 374, 1936.

86. Petraghane, G.: Bul. Off. internat. hyg. 30: 2257, 1938.

87. Velasco, C.: Bol. Inst. Intern. Am. Prolec. Infan. 9: 3, 1936.

88. Armand, M.: Bol. Inst. Intern. Am. Prolec. Infan. 9: 3, 1936.

89. Ordonezdiaz, P. H.: Bol. Inst. Intern. Am. Prolec. Infan. 9: 3, 1936.

90. Suares, L. A.: Bol. Inst. Intern. Am. Prolec. Infan. 9: 3, 1936.

91. Bureau of the Census of the United States.

92. The Register General Statistical Review of England and Wales for the year 1938.

93. Statistica de il cause di morte, 1937.

94. de Pinto, C. E.: Report on Vital Statistics, 1939.

95. Ann. Report of Medical Dept. Sta. Settlements Federated Malay States and Unfederated Malay States, 1938.

96. La Alimentacion, in Chile, 1942, p. 260.

97. Scott, A. C.: Indian J. M. Res. 4: 140, 1916.

98. Maxwell, J. P.: China M. J. 37: 625, 1923.

99. Ogata, M.: Beitrage z. Geburtsh. u. Gynäk. 17: 23, 1911; 18: 8, 1912.

Bosnia,¹⁰⁰ where 3,510 cases were seen in the twelve years previous to 1910. The disease is most frequently found in India among women of the upper and middle classes who practice seclusion or purdah after marriage. It is seldom found among the lower classes who have to work outdoors.

This disease and rickets have the same etiologic factors, viz. vitamin D deficiency and disturbance of calcium metabolism; also no sharp distinction can be drawn between late or adult rickets and osteomalacia. It has been reported¹⁰¹ that among 1,000 children of well-to-do parents whose mothers observe purdah 25 per cent had rickets, whereas among 2,300 children of low caste Hindus only about 5 per cent were affected.

"War Osteopathy," or "Hunger Osteomalacia."—A nutritional disorder which was generally termed "war osteopathy" or "hunger osteomalacia" made its appearance among the peoples of central Europe shortly after World War I. It was common in Austria, Germany and Poland. This disorder was characterized by pains in the back, groins and legs, by a somewhat characteristic gait, by difficulty in climbing stairs and by some tenderness of the bones. The age and sex distribution was peculiar. Beninde¹⁰² stated that there was pronounced susceptibility of adolescents, mainly males; almost no cases occurred between the ages of 20 and 35, whereas the high incidence was in the period from 40 to 60 years, confined almost entirely to women. Hess¹⁰³ states that the condition "developed to a degree and extent such as had never been experienced in the history of medicine. Marked deformities of the spine and the extremities, multiple fractures, and functional disabilities by the thousand, were observed throughout the land." He reasons that from the very close resemblance between this condition and the classic osteomalacia it would seem of advantage to class them as one and the same disorder.

Tetany.—This is a syndrome manifested by sharp flexion of the wrists and ankle joints, muscle twitchings, cramps and convulsions. It is due to abnormal calcium and phosphorus metabolism. It may be associated with

100. Januszewska, G.: Wien. klin. therap. Wchnschr. **17**: 503, 1910.

101. Huchison, H. S., and Shah, S. J.: Quart. J. Med. **15**: 167, 1922.

102. Beninde, M.: Ver. a. d. Geb. d. Medizinalverwaltung **10**: 1, 1920.

103. Hess, A. F.: Rickets, Osteomalacia and Tetany, Philadelphia, Lea & Febiger, 1929.

several conditions, but consideration here is given only to its association with vitamin D deficiency in relation to rickets and osteomalacia. As in rickets, the peak of the incidence of tetany is in late winter and early spring.¹⁰⁴

Tetany has often been noted in cases of rickets and osteomalacia. In one report¹⁰⁵ it was recorded that one fifth of the cases of rickets and one third of their cases of osteomalacia showed signs of tetany. In another

TABLE 4.—Deaths from Rickets

Area Reported	Year	Number of Deaths	References
United States.... .	1933	339	U S Bureau of the Census ⁹¹
	1934	292	
	1935	261	
	1936	270	
	1937	235	
	1938	244	
	1939	143	
	1940	161	
England and Wales. . .	1941	139	Register General Statistical Review of England and Wales for 1938 ⁹²
	1948	493	
	1929	416	
	1930	316	
	1931	461	
	1932	301	
	1933	213	
	1934	180	
	1935	159	
	1936	148	
Italy.....	1937	158	Statistica, 1937 ⁹³
	1938	124	
Malaya States.....	1939,	129	de Pinto ⁹⁴
Colombo, Ceylon.....	1938	21 of 57 hospitalized	Straits Settlements report ⁹⁵
Chile.....	1942	170 of 195 hospitalized	Alimentacion in Chile ⁹⁶

report¹⁰⁶ it was stated that 30 of 63 patients with rickets had tetany, while in another¹⁰⁰ it was noted that tetany occurred in 338 of 3,510 cases of osteomalacia seen in Bosnia.

Tetany in rickets may be the immediate cause of death. This comes about either by the result of heart failure following spastic contraction of the heart muscle or by respiratory failure of cerebral origin. Happily

104. Kassowitz, M.: *Praktische Kinderheilkunde*, Berlin, Springer, 1910. Frankl-Hochwart, L.: *Die Tetanie der Erwachsenen*, Vienna, Haetder, 1907. Japha, A.: *Arch. f. Kinderh.* 42: 66, 1905.

105. Huchison, H. S., and Stapleton, G.: *Brit. J. Dis. Child.* 21: 18, 1924.

106. Stapleton, G.: *Lancet* 1: 1119, 1925.

this result is infrequent, as there are many therapeutic measures available for rapidly controlling the convulsive seizures. Some cases, however, resist all measures.

Reports in recent years on incidence of tetany in various localities are limited as a rule to individual case reports. Snelling and Brown¹⁰⁷ reported 32 cases in 1928 and 28 in 1935 at the Hospital for Sick Children in Toronto, Canada. Hennig¹⁰⁸ observed 79 cases of manifest tetany in central Europe from 1933 to 1937.

VITAMIN B₁ (THIAMINE) DEFICIENCY

Vitamin B₁ (thiamine) deficiency has been known since antiquity by many synonyms: polyneuritis endemica, barbiere (France), loempoe (Java), kakke (Japan and China), taon (Philippines), maladie des sucres (French Antilles), hinchazon (Cuba), michasas or pernieras (Brazil), maladie des jambes (Louisiana).¹⁰⁹

The classic type of beriberi is characterized by symptoms due to damage of the nervous and cardiovascular systems and produces neuritis and heart failure. In the so-called "dry" type of the disease the nervous manifestations are the predominant symptoms, and in the "wet" type the edema of heart failure is the more striking sign. Various combinations may exist. The neuritic form is seen most commonly in the United States¹¹⁰ except in some areas of Louisiana, where classic beriberi occurs.¹¹¹ Infantile beriberi occurs in breast fed infants of mothers with the disease.

Geographically the disease is widespread, occurring endemically or sporadically in all parts of the world. The classic form is common in Asia and Australasia. It occurs with less frequency in Africa, South and Central America, Europe and the United States (table 5). In the latter country about 20 per cent of chronic alcoholic addicts have neuritic manifestations of the disease.¹¹⁰ Infantile beriberi has a death rate of over 90 per cent and is a chief cause of infant death in the Far East.¹¹²

107. Snelling, C. E., and Brown, Alan: *J. Pediat.* 10:167 (Feb.) 1937.

108. Hennig, E.: *Ztschr. f. Kinderh.* 61:379, 1939.

109. Williams, R. R., and Spies, T. D.: *Vitamin B₁ (Thiamine) and Its Use in Medicine*, New York, Macmillan Company, 1938.

110. Scott, L. C., and Herrmann, G. R.: Beriberi ("Maladie des Jambes") in Louisiana, *J. A. M. A.* 90:2083 (June 30) 1928.

111. Jolliffe, Norman: *Quart. J. Studies on Alcohol* 1:74 (June) 1940.

112. Beckman, Harry: *Treatment in General Practice*, Philadelphia, W. B. Saunders Company, 1930.

NICOTINIC ACID DEFICIENCY (PELLAGRA)

Deficiency in niacin (nicotinic acid) or closely related substances results in the disease pellagra. The most prominent symptoms of pellagra are stomatitis, dermatitis, mental changes, gastrointestinal upsets and weakness. Pellagra occurs most commonly in people of poor economic status because of the greater food restrictions in this group. In the United States most of the cases occur in the Southeastern states in the spring and early summer.

From 1933 to 1940 the annual death rates from pellagra in thirteen states of the Southeastern United States varied between 5.1 to 22.4 per hundred thousand of population.¹¹³ In 1941, four years after the discovery that nicotinic acid was the pellagra preventive vitamin, 1,868 deaths were reported from pellagra in the United States.¹¹⁴ Many other reports offer strong evidence that pellagra remains prevalent in the United States. Bean, Spies and Blankenhorn¹¹⁵ estimate that 1 to 2 per cent of all admissions to the medical services of the Lakeside Hospital, Cleveland, and the Cincinnati General Hospital were due to pellagra. Goldsmith¹¹⁶ found evidence of pellagra in 17 per cent of 200 consecutive admissions to the medical services of the Charity Hospital, New Orleans. Many other reports of cases of pellagra both within and without the endemic areas in the United States are summarized in table 6.

Outside the United States the great endemic areas appear to be Egypt, Rumania, Bulgaria and many parts of Africa. Ellinger, Hassan and Tahá¹¹⁷ found that 34.3 per cent of 204 people examined in lower Egypt had signs of pellagra; Clark¹¹⁸ states that 201 cases were admitted to the dermatologic service of the Alexandria Hospital in 1931-1933 and that the incidence at the Cairo General Hospital was 3 to 24 cases per thousand admissions to the medical services. In 1918, 70,000 cases were said to exist in Rumania,¹¹⁹ and in

113. De Kleine, William: *South. M. J.* 35:992 (Nov.) 1942; *Am. J. Pub. Health* 27:595 (June) 1937.

114. Division of Sanitary Reports and Statistics, U. S. Public Health Service, personal communication to the author.

115. Bean, W. B.; Spies, T. D., and Blankenhorn, Marion A.: *The Incidence of Pellagra in Ohio Hospitals*, *J. A. M. A.* 118:1176 (April 4) 1942.

116. Goldsmith, Grace A.: *South. M. J.* 36:108 (Feb.) 1943.

117. Ellinger, P.; Hassan, A., and Tahá, M. M.: *Lancet* 2:755 (Sept. 25) 1937.

118. Clark, Alfred: *J. Trop. Med. & Hyg.* 40:221 (Oct. 1) 1937.

119. Stannus, H. S.: *Trop. Dis. Bull.* 33:729 (Oct.) 1936.

TABLE 5.—*Reports of Vitamin B₁ (Thiamine) Deficiency*

Location	Comment	References
AFRICA		
Brazzaville.....	Report of 12 cases in 1942.....	Nicol, R.: <i>Rev. sc. méd. Afrique Fr.</i> 1 : 81, 1942
Eastern Congo.....	Report of 50 cases in 1940.....	Wilcocks, C.: <i>Trop. Dis. Bull.</i> 37 : 751, 1940
18th Mil. Reg. Fr.....	430 cases observed, 1933-1936.....	Malard, M., and Delprat: <i>Rev. Service de San. & Mil.</i> 106 : 91, 1937
Madagascar.....	Outbreak in some troops in 1937.....	Sanner: <i>Ann. méd. pharm.</i> col. 36 : 840, 1938
Nigeria.....	Common in famine years.....	Summary of Information Regarding Nutrition in the Empire, London, 1939
ASIA		
Burma.....	1,564 cases in 1935.....	McKinley, E. B.: <i>Geography of Diseases</i> , 1935
Burma.....	Endemic.....	Youmans, J. B.: <i>Nutritional Deficiencies</i> , 1941
Brunei.....	High incidence in parturient women and in children, 1935.....	Ann. Rep. Med. Dept. (Brunei) 1935
China.....	Endemic.....	Youmans, J. B.: <i>Nutritional Deficiencies</i> , 1941
China (Shanghai).....	15 per cent of 760 hospital patients admitted for beriberi in 1939.....	Kuo, P. T.: <i>Chinese M. J.</i> 55 : 427, 1939
Hong Kong.....	2.8 per cent of deaths due to beriberi in 1936.....	Ann. Rep. Div. Med. & San. Service, 1936
Hong Kong.....	18 per cent of infants at a welfare center, 1941.....	Fehily, Lydia: <i>J. Trop. Med. & Hyg.</i> 44 : 21, 1941
Hong Kong.....	1,661 deaths due to beriberi in 1938.....	Summary of Information Regarding Nutrition in the Empire, London, 1939
India.....	Endemic.....	Youmans, J. B.: <i>Nutritional Deficiencies</i> , 1941
India (Guntur).....	510 cases (1936-1939) reported.....	Raman, T. K.: <i>J. Indian Med. A.</i> 12 : 50, 1942
India (Visagapatnam).....	200 cases (1937-1940) reported.....	Raman, T. K.: <i>J. Indian Med. A.</i> 12 : 50, 1942
India (Godavari).....	Endemic.....	Aykroyd, W. R., and Krishnan, B. G.: <i>Indian J. Med. Res.</i> 29 : 551, 1941
India (Madras).....	40,000 cases per year (1941).....	Aykroyd and Krishnan, <i>ibid.</i> 29 : 708, 1941
Indo-China.....	3,365 cases in 1935.....	McKinley, E. B.: <i>Geography of Diseases</i> , 1935
North Borneo.....	Sporadic epidemics.....	Ann. Rep. M. Dept. (N. Borneo) 1936
Trengganu.....	1,176 cases treated in 1936.....	Ann. Med. & San. Rept. (Trengganu) 1936
Siam.....	2,000 deaths per year.....	Bull. Health Off. League of Nations 9 : 361, 1940-1941
AUTRALASIA		
Australia.....	8 per cent of 150 infants partially deficient, 1942.....	Clements, F. W.: <i>M. J. Australia</i> , 1942
Celebes.....	3,000 cases, 1933-1934.....	Feischer, D.: <i>Geneesk. Tijdschr. Nederl. Indië</i> 75 : 1975, 1935; Abstr. Nutrition Abstr. & Rev. 6 : 184, 1936

East Indies.....	1,549 cases, 101 deaths in 1931; 1,333 cases, 129 deaths in 1932	Indisch. Verslog., 1933.
Japan.....	Endemic	Youmans, J. B.: Nutritional Deficiencies, 1941
Malay.....	13,828 deaths in 1933; 11,841 deaths in 1934	Ann. Rep. San. Bur. Imp. Jap. Gov., 1937
Nauru.....	Endemic	Youmans, J. B.: Nutritional Deficiencies, 1941
New Guinea and Papua.....	1,262 deaths in 1938	Ann. Rep. of Med. Dept. (Malay), 1938
Philippines.....	Endemic	Farle, K. V.: J. Trop. Med. & Hyg. 44: 142, 1941
Straits Settlements.....	48 deaths in 1940	U. S. Army M. Bull. No. 65
	Epidemics occur	Van Veen, A. G.: Bull. H. O. Leag. of Nations 9: 357, 1940
	1935, 18,614 deaths; 1934, 21,419 deaths; 1933, 18,682 deaths; 1932, 17,173 deaths	Intergov. Conf. of Far Eastern Countries on Rural Hygiene, League of Nations, 1937
	1,262 cases, 121 deaths in 1933	Ann. Rep. Med. Dept. Straits Settlements, 1939
CENTRAL AMERICA		
Central America.....	Endemic	Beckman ¹¹²
Costa Rica.....	43 cases in 1939	Bull. Off. San. for Pan. Am., 1939
EUROPE		
Balkans.....	Sporadic cases occur	McDougall, E. J.: Leag. of Nat. Health Org. Bull., 1939
Hungary.....	Sporadic cases reported	Garavolokvi, K.: Abstr. Nutrition Abstr. & Rev., 1936-1937
Sardinia.....	Sporadic cases occur	Cocchi, C.: Rev. Clin. Pediat. 37: 193, 1939
St. Helena.....	200 cases in 1938	Summary of Information Regarding Nutrition in the Empire, London, 1939
Iceland.....	16 cases seen in 1933	Kilka, P. V. G.: Laeknabl. 6/8, 18, 1933; Abstr. Nutrition Abstr. & Rev. 3: 82, 1933
SOUTH AMERICA		
South America.....	Sporadic cases occur	Cecil, R. L.: Textbook of Medicine, 1942
Brazil.....	Endemic	Zimmerman, H. M.: Nelson's Loose-Leaf Medicine
Argentina.....	Sporadic cases	Cossio, P., and Moia, B.: Dia méd. 9: 1148, 1937
British Guiana.....	Local epidemic 1934	Report of Surg. Gen. (British Guiana), 1934
UNITED STATES and CARIBBEAN		
United States.....	49 deaths in 1941	U. S. Bureau of the Census, 1942
United States.....	20 per cent of alcoholic addicts	Jolliffe ¹¹¹
Louisiana.....	Endemic in certain areas	Scott and Herrmann ¹¹⁰
West Indies.....	Occurs	Williams and Spies: ¹⁰⁸ Beckman ¹¹²
Trinidad.....	87 cases in 2,422 consecutive admissions	Farle, K. V.: J. Trop. Med. & Hyg. 44: 150, 1941

TABLE 6.—Incidence of Pellagra

Area and Date	Incidence	References and Comment
13 Southeastern states, U. S., 1928-1940	Death rates per 100,000 population varied between 6.1 and 22.4	De Kleine ¹¹¹
United States, 1933-1941	Total deaths from pellagra in United States varied from 3,436 to 1936	Sanitary Reports ¹¹²
Ohio Hospitals, U. S., 1942	Pellagra accounted for 1 to 2% of admissions to medical wards	Bean, Spies and Blankenhorn; ¹¹³ noteworthy because outside endemic area
Charity Hospital, New Orleans, 1943	Pellagra found in 17% of 200 consecutive admissions to medical wards	Goldsmith ¹¹⁴
Charity Hospitals, New Orleans and Shreveport, La., 1937-1941	3 to 21 deaths yearly in these 2 hospitals	Love, B. O.: New Orleans M. & S. J. 95: 407, 1943; 58 to 163 cases admitted yearly
Michigan, 1940	Signs and symptoms of pellagra frequent in Northern states, especially in the alcoholic	Field, H., Jr.: New England J. Med. 223: 307, 1940; states that disease is commonly overlooked in the north
California, 1928-1935	Death rates varied from 0.72 to 1.36 per 100,000 population	Smith, C. E., and Stevens, I. M.: Am. J. Hyg. 27: 590, 1933
Indiana, 1934	Reports 11 cases	Fouts, P. J., and Zerfas, L. G.: J. Indiana State M. A. 27: 196, 1939; all cases admitted to Indianapolis General Hospital
Kentucky, 1939	Reports 41 cases	Kooser, J. H., and Blankenhorn, M. A.: J. A. M. A. 112: 2581, 1939; all cases occurred in county (Perry)
Alabama, 1937	50 cases admitted to Hillman and T. C. I. Hospitals, Birmingham	Spies, T. D.; Chinn, A. B., and McLester, J. B.: J. A. M. A. 108: 853, 1937
Alabama, 1939	Reports 977 cases of multiple B vitamin deficiency (see riboflavin table)	Spies, T. D.; Vilter, R. W., and Ashe, W. F.: J. A. M. A. 113: 931, 1939; states that multiple deficiency states are very common
Canada, 1942	Reports 1 case	Quentin, T. J.: Canad. M. A. J. 47: 464, 1942
England and Wales, 1923-1938	77 deaths reported in 10 year period	Registrar General's Statistical Review of England and Wales for the years 1938, New Annual Series, No. 18, H. M. Stationery Office, London
Northern Ireland, 1942	16 cases	Deeny, J.: Brit. M. J. 1: 157, 1942; 16 patients with suggestive skin or gastric symptoms were relieved with niacin
England, 1934-1939	8 cases	Davies, J. H. T., and McGregor, H. G.: Brit. J. Dermat. & Syph 51: 51, 1939
England, 1941	1 case	Davis, E., and Hinden, E.: Lancet 1: 110, 1941; patient was alcoholic
Scotland, 1940	1 case	Robinson, D. S.: Edinburgh M. J. 27: 81, 1940
Italy, 1937	74 deaths in 1937	Statistica delle Cause di Morte nell'Anno 1937
Transcaucasia, 1933	30,000 to 50,000 cases estimated	Natch: ¹¹⁵ total population, 1,300,000
Bulgaria	Author saw personally 228 cases in 35 years of practice	Molov; ¹¹⁶ the most important avitaminosis in Bulgaria is pellagra
Rumania, 1918	70,000 cases estimated	Stannus; ¹¹⁷ source of figure is not clear in reference
Belgium, 1939	1 case	Van Borgert, L., and Vanden Barche: Bull. Acad. 4: 409, 1939
Switzerland, 1938	2 cases	Bickel, G.: Schweiz. med. Wchnschr. 68: 1159, 1938
Norway, 1934-1939	18 cases	Kjelland, J.: Nordisk. Med. 1: 693, 1939
Netherlands, 1938	10 cases	DeLangen, O. D.; Bowsijk, J. C., and van Nieuwenhuizen, O. L. O.: Nederl. tijdschr. v. geneesk. 72: 4970, 1938
Sweden, 1939	5 cases	Mindus, E.: Nordisk. Med. 3: 2477, 1939; "many ill defined cases seen"
Germany, 1939	1 case	Sahn, H.: Munchen. med. Wchnschr. 56: 882, 1939
Spain, 1937-1938	"Many" in Madrid during and after Spanish Civil War	Jiminez: Garcia, F., and Grande Covian, F.: Rev. clin. española, 1: 313, 1940

Rumania, 1924.....	Death rate 11.8 per 100,000.....	Jonesco-Mihalesti, Culca and Oulca, ¹²⁰
Rumazlia (Moldovia), 1938.....	2 cases in 4 families comprising 33 persons	Enescu, M., and Rodenschi, A.: Abstr. Zentralbl. i. d. ges. Hyg. 41:250, 1938
Brazil, 1930-1937.....	114 cases at Recife, 16 cases in rest of Brazil	Da Costa and Casiro ¹²¹
Argentina, 1941.....	8 cases reported to 1941.....	Biettreich, ¹²² pellagra is rare in Argentina
Chile, 1942.....	110 cases reported in Santiago.....	Alessandri, ¹²⁴ states that there are now 3,000 cases in Chile
Africa, 1937.....	Describes 26 cases occurring in 1934-1935 in Nairobi Hospital, Kenya Colony in children	Trowell ¹²³ states that the disease is endemic on east and west coasts and in Central Africa
Africa, 1932-1933.....	145 total	Stannus, ¹¹⁹ figures collected from annual medical reports of colonies
Africa, 1937-1938.....	171 cases at Aba and Lagos, Nigeria, in 744 persons examined	Moore, D. F.: J. Trop. Med. & Hyg. 42:109, 1939
Egypt, 1937.....	Found pellagra in 34.3% of 204 people examined in lower Egypt	Ellinger, Hassan and Tabá: ¹¹⁷ pellagra is rare in upper Egypt but does occur
Egypt, 1931-1933.....	Rate at Cairo General Hospital was 3 to 24 cases per 1,000 admissions, depending on the season	Clark ¹¹⁸
Egypt, 1938.....	15 cases	Alport, A. C.: Chalioungul, P., and Hanna, G.: Lancet 2:1460, 1938
India.....	Pellagra is very frequent in a large percentage of infants	Aykroyd ¹²⁵
India, 1942.....	Widespread	Batra: ¹²⁶ all types of deficiency disease are seen, but pellagra is most widespread
India, 1941.....	Describes 10 cases.....	Carruthers ¹²⁸
India, 1940.....	Describes 25 cases; incidence 0.65% of admissions to medical wards	Raman: ¹²⁸ Vizagapatam is an endemic focus of pellagra
India, 1942.....	Saw 6 cases in 18 months.....	Ahmed: Indian M. Gaz. ¹²⁸
India, 1939.....	Describes 5 cases; 12 cases seen at the medical school yearly	Sen Gupta, Rai Chaudhuri, Chaudhuri and Napier ¹²⁸
India, 1942.....	20 cases	Ahmed: J. Indian M. A.: ¹²⁸ present in upper provinces
India, 1940.....	"Frequent"	Goodall: ¹²⁶ in India cases of pellagra are frequently met
Straits Settlements and Malaya, 1937.....	64 cases in 10 years with 1 death	Napier ¹²⁸ thinks pellagra is frequent in India but is not diagnosed
Malaya, 1935.....	3 cases	Ann. Rep. M. Dept. Straits Settlements, Fed. Malay States and United Malay States, 1938
Straits Settlements, 1932.....	2 cases	Landor, J. V., and Pallister, R. A.: Tr. Roy. Soc. Trop. Med. & Hyg. 29:121, 1935; disease sporadic in Malaya
Hong Kong, 1932.....	24 cases	Stannus, ¹¹⁹ quoting reports of medical departments of British colonies
Trinidad, 1933.....	1 case	Wyjasnowsky ¹²⁶
St. Christophers, 1932.....	1 case	Yang and Huang: ¹²⁷ occurred in army camp
Antigua, 1933.....	2 cases	Yu: ¹²⁷
British Honduras, 1933.....	1 case	Wilson ¹²⁷
Bahamas, 1928-1932.....	404 cases at Tashkent.....	Itchik: ¹²⁸
Russian Turkistan, 1934.....	20 cases at Tashkent.....	Morris, Hwang and Kuo: ¹²⁷ all from 1 war refugee camp
China, 1934.....	30 cases	Urabe: ¹²⁷
Manchuria, 1934.....	3 cases	
Korea, 1929.....	Present in leprosy colonies.....	
Japan, 1926.....	72 cases reported in Japan to 1925.....	
China, 1941.....	40 cases	
Korea, 1939.....	39 cases	

1934 the death rate in Rumania is given as 11.8 per hundred thousand of population.¹²⁰ The data on Bulgaria are not so definite, but Molov¹²¹ believes that pellagra is the most common avitaminosis in that country. Trowell¹²² states that pellagra is endemic among the children in certain tribes on the east and west coasts and in Central Africa. Nauck¹²³ makes the astonishing estimate that in Transcaucasia in 1933 there were 30,000 to 50,000 pellagrins in a population of 1,300,000, or a case incidence of 23 to 38 per cent. Alessandri and his collaborators¹²⁴ estimated the number of cases in Chile in 1942 to be 3,000. Smaller numbers of cases have been reported from India,¹²⁵ Russia,¹²⁶ China,¹²⁷ Japan,¹²⁸ South America,¹²⁹ and many of the British colonies.¹¹⁰ Exclusive of Spain, Italy and the Balkans, the disease seems to be only sporadic in Europe.

ARIBOFLAVINOSIS

Ariboflavinosis is a disease due to deficiency of the water soluble vitamin riboflavin. It is characterized by the development of cracks in the skin at the corners of the mouth (cheilosis), a greasy eruption of the skin, changes in the tongue and keratitis, caused by an invasion of the cornea by blood vessels.

Because of the recent description of the disease, information on its incidence is relatively scanty. In 1938 the Oden and Sebrell¹⁸⁰ felt that the disease

120. Jonesco-Mihaiessti, C.; Cuica, A., and Cuica, M.: Arch. Roumaines de path. exper. et microbiol. **8**: 422, 1932.

121. Molov, V.: Liječn Vjern. **59**: 397, 1937; abstr. Zentralbl. f. d. ges. Hyg. **41**: 409, 1938.

122. Trowell, H. C.: Arch. Dis. Childhood **12**: 193 (Aug.) 1937.

123. Nauck, E. G.: Beihefte z. Arch. f. Schiffs- u. Tropen-Hyg. **37**: 85, 1933.

124. Alessandri, H.; Garcia Palazuelos, P., and Lerner, M. J.: Rev. argent. d. Dermatosisif. **26**: 25, 1942.

125. Aykroyd, W. R.: Bull. Off. internat. d. hyg. pub. **29**: 2388, 1939. Batra, B. L.: Indian M. Gaz. **77**: 269 (May) 1942. Carruthers, L. B.: Tr. Soc. Roy. Med. & Hyg. **35**: 21, 1941. Raman, T. K.: Indian J. M. Research **27**: 743 (Jan.) 1940. Ahmed, N.: Indian M. Gaz. **77**: 140 (March) 1942. Sen Gupta, P. C.; Rai Chaudhuri, M. N.; Chaudhuri, R. N., and Napier, L. E., *ibid.* **74**: 143 (March) 1939. Ahmed, N.: J. Indian M. A. **12**: 1 (Oct.) 1942. Goodall, J. W. D.: Indian M. Gaz. **75**: 147 (March) 1940. Napier, L. E., *ibid.* **74**: 137, 1939.

126. Wyjasnowsky, J.: Arch. f. Schiffs- u. Tropen-Hyg. **38**: 31, 1934.

127. Yang, C. S., and Huuung, K. K.: Chinese M. J. **48**: 701, 1934. Yu, K. Y., *ibid.* **48**: 724 (Aug.) 1934. Wilson, R. M., *ibid.* **39**: 661, 1926. Morris, H. H.; Hwang, M. S., and Kuo, P. T., *ibid.* **57**: 427, 1941. Urabe, K.: Jap. J. Dermat. u. Urol. **47**: 2, 1940.

128. Itoh, N.: Far East. Assn. Trop. Med., Tr. 6th Biennial Cong. Tokyo **1**: 315, 1925.

129. Da Costa, V. F., and Castro, M.: Rev. Assoc. paulista de med. **11**: 363, 1937. Bieltreich, R. A.: Rev. méd. latino-am., **26**: 351, 1941. Alessandri, Garcia Palazuelos and Lerner.¹²⁴

130. Oden, J. W.; Oden, L. H., Jr., and Sebrell, W. H.: Pub. Health Rep. **54**: 790 (May 12) 1939.

might be common in the southern United States. Spies, Bean, Vilter and Huff¹³¹ believe it to be the most common deficiency disease in the United States. Goldsmith¹³² found an incidence of 34 per cent in 200 consecutive admissions to the medical services of Charity Hospital, New Orleans. Wiehl and Kruse⁶ found that 75.8 per cent of pupils in a school in the East Side of New York City had signs of mild riboflavin deficiency, as did 34.4 per cent of a group of 143 WPA employees. Kruse's figures must be interpreted with care, since the diagnoses were made entirely on the changes found in the eyes, which by themselves are not specific of riboflavin deficiency. Nevertheless the reports cited plus additional ones cited in table 7 warrant the conclusion that the disease occurs in many parts of the United States and is very prevalent in the South.

Reports from other parts of the world are even more fragmentary than those from the United States. The disease has been reported in England¹³³ and is probably widespread in India,¹³⁴ China,¹³⁵ Malaya¹³⁶ and Africa.¹³⁷

VITAMIN C DEFICIENCY

Scurvy is a metabolic disease resulting from a deficiency of vitamin C and characterized by a general debility, progressive anemia, a hemorrhagic tendency and skeletal changes of infants and children as the result of arrestment of bone development and hemorrhage.

The disease is of worldwide occurrence. Case studies and group surveys have been reported from Africa,¹³⁸ China,¹³⁹ Australia¹⁴⁰ and its territories,¹⁴¹ Malaya,¹⁴²

131. Spies, T. D.; Bean, W. B.; Vilter, R. W., and Huff, W. E.: *Am. J. M. Sc.* **200**: 697 (Nov.) 1940.

132. Goldsmith, Grace A.: *South. M. J.* **36**: 108 (Feb.) 1943.

133. Scarborough, Harold: *Brit. M. J.* **2**: 601 (Nov. 21) 1942.

134. Aykroyd, W. R., and Kishnan, B. G.: *Indian J. M. Research* **24**: 411 (Oct.) 1936. Aykroyd, W. R., and Verma, O. P.: *Indian M. Gaz.* **77**: 1, 1942. Verma, O. P., *ibid.* **77**: 471 (Aug.) 1942.

135. Hou, H. C.: *Chinese M. J.* **59**: 314, 1941.

136. Laudor, J. V., and Pallister, R. A.: *Tr. Roy. Soc. Trop. Med. & Hyg.* **29**: 121, 1931.

137. Pursell, F. M.: *Tr. Roy. Soc. Med. & Hyg.* **35**: 323, 1942. Barlovatz, A.: *Ann. Soc. belge de méd. trop.* **21**: 13, 1940.

138. Hofmeyr, H. O.: *Proc. Staff Meet., Mayo Clin.* **16**: 644 (Oct. 8) 1941. Henson, J.: *South African M. J.* **12**: 918 (Dec. 24) 1938; *Ann. Rep. M. Services, Nigeria, 1936-1937*. Drogoz & Henric: *Ann. Med. Pharm., Colon* **35**: 1093, 1937. Dry.¹³⁴

139. Morgan, Julia, and Gault, A. S.: *Chinese M. J.* **60**: 141 (Aug.) 1941.

140. *Health (Australia)* **15**: 15, 140 (Nov.) 1937.

141. *Army M. Bull.* No. 65, 1943, p. 32.

142. *Ann. Rep. M. Dept., Straits Settlements, 1929-1935.*

TABLE 7.—Incidence of Riboflavin Deficiency

Area and Year	Incidence	References and Comment
Georgia, 1939.....	3 cases	The Odens and Sebrell: ¹³⁰ all had cheilosis
New York, 1939.....	15 cases	Jolliffe, W.; Fern, H. D., and Rosenblum, L. A.: New England J. Med. 221: 24, 1939; all had cheilosis
Georgia, 1938.....	6 cases	Sydenstricker, V. P.; Geeslin, L. E.; Templeton, C. M., and Weaver, J. W.: J. A. M. A. 113: 1067, 1939; all had cheilosis
Alabama, 1939.....	977 cases of multiple B vitamin deficiency..	Spies, T. D.; Vilter, R. W., and Ashe, W. F.: J. A. M. A. 113: 931, 1939
Alabama, 1940.....	241 cases in infants and children	Spies, Bean, Vilter and Huff: ¹³¹ believe ariboflavinosis to be the most common clinical deficiency disease
Georgia, 1940.....	45 cases	Sydenstricker, V. P.; Sebrell, W. H.; Cleckley, H. M., and Kruse, H. D.: J. A. M. A. 114: 2437, 1940; patients had eye lesions responding to riboflavin therapy
Georgia, 1940.....	9 cases	Kruse, H. D.; Sydenstricker, V. P.; Sebrell, W. H., and Cleckley, H. M.: Pub. Health Rep. 55: 157, 1940; eye lesions
New York City, 1941.....	Mild deficiency in 4.7% of 350 well-to-do children; mild deficiency in 75.8% of 495 pupils from low income groups; mild deficiency in 34.4% of 143 WPA employees	Wiehl and Kruse: ⁹ diagnoses made purely on the basis of eye examination
New Orleans, 1942.....	93 of 200 individuals admitted consecutively to medical wards of Charity Hospital had some evidence of riboflavin deficiency	Goldsmith: ¹³² finds ariboflavinosis to be the most common deficiency
India, 1936.....	41 cases of "angular stomatitis".....	Aykroyd and Kishman: ¹³⁴
India, 1942.....	13 cases	Aykroyd and Verma: ¹³⁵ "superficial keratitis"
India, 1942.....	50 cases	Verma: ¹³⁶ "superficial keratitis"
Malaya, 1931.....	Prevalent in prisons at Singapore and Johore	Landon and Fallister: ¹³⁸ syndrome characterized by cheilosis, glossitis, scrotal dermatitis and combined degeneration of the spinal cord
China, 1941.....	47.9% of 186 refugees had riboflavin deficiency	Hou: ¹³⁵
Africa, Gold Coast, 1942.....	6 cases	Pursell: ¹³⁷ cases chiefly glossitis
Africa, Belgian Congo, 1940.....	Many types of glossitis and angular stomatitis are seen among the natives of the Belgian Congo	Barlovaatz: ¹³⁷
England, 1942.....	3 cases	Scarborough: ¹³⁸ 3 cases of keratitis responding to riboflavin deficiency

TABLE 8.—*Reports of Vitamin C Deficiency*

Country and Year	Incidence of Scurvy Reported	Comment	References
Rhodesia, South Africa, 1932.....	80%	10,000 native mine employees.....	Dry ¹⁵⁴
Lausanne, France, 1933.....	90%	Survey of school children during winter months by blood vitamin C determinations; attributed to drop in milk and potato content of diet	Messerli and Helmann ¹⁵⁵
Bucharest, Rumania, 1941.....	90%	Survey among school children during winter months by blood studies; incidence due to inadequate winter diet	Mezincesco ¹⁵⁷
Nashville, Tenn., 1940.....	50%	Study of 500 children attending pediatric clinic by blood analysis technic	Milam ¹⁵⁶
Chaco area, Uruguay, 1939.....	3.4 to 15.5%	Observed incidence among hospital patients of military and civilian sources respectively	Quiroz ¹⁵³
Switzerland, 1940.....	57%	94 soldiers studied by blood analysis.....	Gander and others ¹⁵⁷
Switzerland, 1942.....	38%	100 civilians of all social and age groups employed in antiaircraft corps	Barrelet ¹⁵⁸
Prague, Czechoslovakia, 1939.....	10%	180 school children studied by blood assay.....	Bytch ¹⁵⁹
New York City, 1941.....	6.7%	A selected group as determined by blood analysis	Wiehl and Kruse ⁶
South Carolina, 1942.....	1.5%	400 citizens of small mill village as determined by blood studies	Croft and Snorf ¹⁶⁰
England, 1942.....	Not significant	Selected groups of school children and medical students as studied by blood assay	Francis and Wormald; ¹⁶¹ Harris ¹⁶¹

the Philippines,¹⁴³ Czechoslovakia,¹⁴⁴ France,¹⁴⁵ Norway,¹⁴⁶ Rumania,¹⁴⁷ Spain,¹⁴⁸ Switzerland,¹⁴⁹ the Faroe Islands,¹⁵⁰ Greenland,¹⁵¹ the United States¹⁵² and South America.¹⁵³ The endemic or epidemic proportions of the disease depend on many factors. In 1932 a report from Rhodesia¹⁵⁴ revealed that 80 per cent of 10,000 natives studied had clinical evidence of scurvy. The crowded housing, increased incidence of infectious diseases, chronic fatigue and native customs of preparation of food were attributed as causative factors. In several studies where the incidence reported has been based on the demonstration of low blood vitamin C levels, in selected groups, the prevalence of hypo-vitamin C appears alarming. During the winter of 1937-1938 among school children studied in Lausanne, France,¹⁵⁵ 90 per cent had low blood levels. A group of school children studied during the winter of 1941 in Bucharest, Rumania,¹⁴⁷ revealed low blood levels in 90 per cent. The authors independently attribute this high incidence to the inadequacy of the winter diet to furnish vitamin C. Among 500 children seen in a pediatric clinic in Tennessee in 1940, 50 per cent had low blood levels for vitamin C.¹⁵⁶ A study among hospital cases in Uruguay¹⁵³ in 1939 revealed an incidence of 15.5 per cent among the civilian population and 3.4 per cent among the soldiers. In 1940 among a group of 94 Swiss soldiers¹⁵⁷ whose enlistment period was in excess of nine months, 57 per cent

143. League of Nations, Health Organization, Intergovernmental Conference on Nutrition, Geneva, 1937.

144. Charvat, J.: Bull. Office internat. d'hyg. pub. **30**: 591 (March) 1938. Bytch.¹⁵⁹

145. Ann. Rep. Internat. Health Div. Rockefeller Foundation, 1941, p. 142. Messerli and Heimann.¹⁵⁵

146. Langfeldt, E.: Nord. med. tidskr. **15**: 244, 1938.

147. Mezincesco, M. D.: Ztschr. f. Vitaminforsch. **11**: 376, 1941.

148. Robinson, W. D.; Janney, J. H., and Grande Covian, Francisca. J. Nutrition **24**: 557 (June) 1942.

149. Gander and others.¹⁵⁷ Barrelet.¹⁵⁸

150. Wagner, K. H.: Deutsche med. Wchnschr. **67**: 1232, 1941.

151. Bøje, O.: Nord. Med. **1**: 740-743, 1939; abstr. Chem. Zentralbl. **8**: 1224, 1941.

152. Minot, A. S.; Dodd, Katharine; Keller, Margaret, and Frank, Helen: J. Pediat. **16**: 717 (June) 1940. Overstreet, R. M.: Northwest. Med. **37**: 175 (June) 1938. Wiehl and Kruse.⁴

153. Quiroz, J. D: Bull. de la Oficina Sanitaria Panamericanos **78**: 55, 1939.

154. Dry, T. J.: Proc. Staff Meet., Mayo Clin. **7**: 309 (May 25) 1932.

155. Messerli, F. M., and Heimann, F.: Rev. d'hyg. **60**: 20 (Jan.) 1938.

156. Milam, D. F.: Am. J. Pub. Health **32**: 406 (April) 1942.

157. Gander and others: Ztschr. f. Vitamin. **11**: 121-128, 1941.

had blood determinations at deficiency levels, while among a group of 100 civilians¹⁵⁸ studied in 1942, 38 per cent demonstrated low blood levels.

Less alarming figures have been reported from similar surveys, utilizing blood level determination, among selected groups. In Prague,¹⁵⁹ in 1939, 10 per cent of 180 school children between the ages of 12 and 20 years had low blood levels. In New York City,⁶ in 1941, 6.7 per cent of a selected group were deficient. In South Carolina,¹⁶⁰ in 1942, 1.5 per cent of 400 people studied in a mill village were also demonstrated to have low blood vitamin C levels. In England,¹⁶¹ comparative studies done in 1939 and 1942 among selected school children and medical students revealed "no significant incidence of scurvy" and no increase in the occurrence rate since the onset of World War II, although the determined blood levels were on the average lower for the latter study period.

In summary it would appear that vitamin C deficiency is of worldwide occurrence in significant numbers of people. Although low blood levels of vitamin C may and do occur without evident manifestations of scurvy, this finding indicates at least an intake of vitamin C below that necessary to maintain the individual's body reserves at the highest level.

VITAMIN K

Vitamin K deficiency manifests itself as a tendency to hemorrhage, brought about by a lowered prothrombin level of the blood. It is believed that the normal human adult can dispense with this vitamin in the diet because of synthesis by bacteria in the intestine. It follows and is supported by clinical findings that K avitaminoses will be found only in the newborn before the bacterial flora has become established and in adults when there is interference with fat absorption.

A tendency to hemorrhage is not a proof of vitamin K deficiency, but it has become well established that this vitamin is of value in preventing hemorrhagic disease of the newborn and the bleeding of obstructive jaundice and a number of other conditions.

158. Barrelet, P.: *Schweiz. med. Wchnschr.* **72**:796 (July 18) 1942.

159. Bytch, L.: *Rev. franç. de pediat.* **15**:188, 1939.

160. Croft, J. D., and Snorf, L. D.: *Am. J. M. Sc.* **108**:403 (Sept.) 1939.

161. Francis, G. E. C. and Wormall, A.: *Lancet* **1**:647 (May 30) 1942. Harris, L. J., *ibid.* **1**:642 (May 30) 1942.

TABLE 9.—Occurrence of Vitamin K Deficiency

Area, Year	Condition	Incidence or Number of Cases	Comment	References
United States 1941	Hemorrhagic disease of newborn	Untreated, 11 of 26; K to mother during labor, 10 of 53; K to mother before labor, 3 of 23	Pray, L. G.; McKeown, H. S., and Pollard, W. E.: <i>Am. J. Obst. & Gynec.</i> 42: 886, 1941
United States 1941	Retinal hemorrhage	Untreated, 56 of 223, K to mother during labor, 34 of 223; K to mother before labor, 3 of 50	Maumenee, Hellman and Shettles ^{101b}
United States 1941	Hemorrhagic disease of newborn	Untreated, expectancy 5 cases; treated, 0 of 556	Javert, C. T., and Macri, C.: <i>Am. J. Obst. & Gynec.</i> 42: 416, 1941
United States 1940	Death from hemorrhagic disease of newborn	Untreated, 2.3%; treated, 0.29%	Deaths (total) 4.1% and 1.6% respectively	Hellman, L. M.; Shettles, L. B., and Eastman, N. J.: <i>Am. J. Obst. & Gynec.</i> 40: 844, 1940
United States 1940	Hemorrhage or birth injury	Untreated, 23 of 219; treated, 4 of 400	Waddell and Lawson ^{101a}
United States 1940	Prothrombin deficiency	111 of 189	
United States 1940	Hemorrhagic disease of newborn	22 cases	Responded to K	Poncher, H. G., and Kato, Katsuji: <i>J. A. M. A.</i> 115: 14, 1940
United States 1939	Hemorrhagic disease of newborn	7 cases	Responded to K	Waddell, W. W., Jr., and Guerry, DuPont: <i>J. Pediat.</i> 15: 802, 1939
United States 1939	Hemorrhagic disease of newborn	1 case	Decreased clotting time in 10 of 10	Waddell, W. W., Jr., and Guerry, DuPont: <i>J. A. M. A.</i> 112: 2259, 1939
United States 1940	Hypoprothrombinemia	41 cases	Treated successfully; 8 with liver damage did not respond	Andrus, P. M., and Lord, J. W., Jr.: <i>Ann. Surg.</i> 112: 788, 1940
United States 1940	Hypoprothrombinemia	39 cases	Treated successfully; 6 with liver damage did not respond	Weir, J. F.; Butt, H. R., and Snell, A. M.: <i>Am. J. Digest. Dis.</i> 7: 486, 1940
United States 1940	Hypoprothrombinemia	20 cases	All except those with liver damage treated successfully; 7 with hem- orrhagic bleeding stopped	Norcross, J. W., and McFarland, M. D.: <i>J. A. M. A.</i> 115: 2156, 1940
United States 1940	Hypoprothrombinemia	28 cases	Treated successfully; 18 did not respond many of these had liver damage	Pohle, F. J., and Stewart, J. K.: <i>J. Clin. Investigation</i> 19: 365, 1940

United States 1940	Hypoprote thrombinemia	17 cases	Treated successfully; 3 with liver damage did not respond	Butt, H. R.; Snell, A. M.; Osterberg, A. E.; and Boll- man, J. L.: Proc. Staff Meet., Mayo Clin. 15: 60, 1940
United States 1940	Hypoprote thrombinemia	10 cases	9 responded; 3 of these had bleeding which stopped	Rhoads, J. E., and Fliegelman, M. T.: J. A. M. A. 114: 400, 1940
United States 1939	Hypoprote thrombinemia in obstructive jaundice	5 cases	Responded to K	Stewart, J. D., and Rourke, G. M.: New England J Med. 221: 403, 1939
United States 1939	Hypoprote thrombinemia in obstructive jaundice	12 cases	Responded to K	Stewart, J. D.: Ann. Surg. 109: 538, 1939
United States 1940	Hemorrhage after operation Bleeding in obstructive jaundice	4 cases 11 cases	Responded to K Responded to K; 5 patients with liver dam- age did not respond	Aggeler, P. M.; Lucia, S. P., and Goldman, L.: Proc. Soc. Exper. Biol. & Med. 43: 689, 1940
Scotland 1940	Intercranial hemorrhage	1 to 2%	85% die in first 3 days; 25% of survivors have motor or mental involvement	Macpherson, A. I. S.; McCallum, E., and Haultain, W F. T.: Brit. M. J. 1: 839, 1940
	Hypoprote thrombinemia	67 cases	K raised above danger point (to 36 babies and to 31 mothers during or before labor)	
Scotland 1939	Hemorrhagic tendency with jaundice	4 cases	Responded to K	Illingsworth, C. F. W.: Lancet 1: 1031, 1939
Denmark 1941	Hemorrhagic disease of newborn	65 cases	Responded to K	Dam, H., and Plum, P.: Monatsschr. f. Kinderh 87: 55, 1941
Denmark 1940	Hemorrhagic disease of newborn	31 cases	Responded to K	Plum, P., and Dam, H.: Ugesk. f. læger, 102: 1029, 1940
Denmark 1939	Hemorrhagic disease of newborn	4 cases	2 responded to K	Dam, H.; Tage-Hansen, E., and Plum, P.: Ugesk. f læger 101: 886, 1939
Sweden 1940	Bleeding in obstructive jaundice	4 cases	Responded to K	Hedenstedt, S.: Nord. Med. 6: 789, 1940
Canada 1940	Bleeding in obstructive jaundice	17 cases	Responded to K	Townsend, S. R., and Mills, E. S.: Canad. M. A. J. 43: 541, 1940
Canada 1939	Bleeding in obstructive jaundice	10 cases	9 responded to K	Townsend, S. R., and Mills, E. S.: Canad. M. A. J. 41: 111, 1939
Germany 1939	Bleeding in obstructive jaundice	1 case	Responded to K	Koller, F., and Wahrman, F.: Klin Wchnschr. 18: 1038, 1939

Most cases of hypoprothrombinemia except those which are due to liver damage have been found to respond to vitamin K.

Avitaminosis K appears to have been studied most extensively in the United States, in Denmark and in the British Isles. Very little information is available from other sections of the world. By far the highest incidence is in the newborn; other cases are negligible in comparison. Estimates of prothrombin deficiency in very young infants range as high as 60 per cent,^{161a} and an incidence of retinal hemorrhage as high as 25 per cent has been observed.^{161b}

NUTRITIONAL ANEMIA

The term "nutritional anemia" is restricted to the anemia resulting from insufficient dietary intake of iron. Anemias indirectly arising from other nutritional deficiency such as that which accompanies scurvy, pellagra or hypoproteinemia are not included here.

Nutritional anemia cannot be regarded as a clearly defined clinical entity. Standards of optimal hemoglobin concentration and optimal red blood cell count for persons of each age, sex or race are not generally agreed on.⁶ Moreover, certain normal physiologic functions such as pregnancy, pubescence, catamenia and the menopause materially alter the blood picture in so complex a manner that the definition of the norm for these special states is uncertain.¹⁶² The situation is further complicated by the fact that other causes of anemia such as chronic latent blood loss, local infection or tuberculosis may be readily overlooked in large scale investigations.

The clinical features of nutritional anemia are likewise not very clearcut. The dietary history affords the most pertinent positive information. In evaluating the dietary history, local variations in the iron content of foods must be kept in mind. The symptoms are somewhat generalized and include lack of energy, headache, vertigo, dyspnea and palpitations. In children, behavior difficulties such as failure to concentrate and

161a. Waddell, W. W., Jr., and Lawson, G. M.: Hemorrhagic Diathesis of the Newborn, *J. A. M. A.* **115**:1416 (Oct. 26) 1940.

161b. Maumenee, A. E.; Hellman, L. M., and Shettles, L. B.: Factors Influencing Plasma Prothrombin in the Newborn Infant, *Bull. Johns Hopkins Hosp.* **68**:158 (Feb.) 1941.

162. Jolliffe, Norman; McLester, J. S., and Sherman, H. C.: The Prevalence of Malnutrition, *J. A. M. A.* **118**:944 (March 21) 1942.

physical indolence are observed. The condition is commonly accompanied by no distinct symptoms whatever.

Physical findings include pallor, loss of skin turgor, suboptimal weight and reduced muscle tone. In advanced cases a soft apical systolic murmur may be heard and the pulse is rapid and of poor quality.¹⁶³

Most often, however, the diagnosis rests solely on laboratory findings. Reznikoff states that, "hematologically, the striking features of iron deficiency from any cause are the relatively marked decrease of hemoglobin compared to the red blood cell reduction and the small size of the cells, giving a low volume index, usually less than 0.75."¹⁶⁴

Recent studies have been concerned both with the development of adequate diagnostic standards and with the determination of the prevalence and distribution of the deficiency. Despite numerous fairly elaborate studies, only a beginning has been made. In table 10 there have been summarized those studies of the past decade which afford epidemiologic data concerning nutritional anemia. The groups studied vary widely and include preschool children, school children, pregnant women and general populations. Standards for the determination of deficiency are frequently not stated and the stated standards vary widely from survey to survey. Moreover, the inherent error in the several laboratory procedures employed in the respective surveys is not at all comparable, although in all instances it is admittedly great. For these reasons each of the recorded studies must be regarded as a distinct source of information bearing on the special group, and no general statistical summary is warranted.

Disregarding these limitations, we may observe from isolated studies that at least in certain communities nutritional anemia should be given close consideration. Thus, about 50 per cent of 2,400 children studied in Pennsylvania in 1939 were anemic. In Michigan 26.6 per cent of 158 pregnant women were found anemic, and in Boston 16 per cent of adults studied were anemic. In New York City 72 per cent of 325 pregnant women were anemic. In Florida in 1939 more than

163. Osler's Textbook of Medicine, ed. 14, H. S. Christian, editor, New York, D. Appleton & Co., 1942.

164. Cecil, R. L.: A Textbook of Medicine, ed. 5, Philadelphia, W. B. Saunders Company, 1942, p. 1071.

50 per cent of 620 school children were found to have subnormal hemoglobin. In Scotland, in 1939, 32 per cent of children and 45 per cent of adults examined were anemic, and in Madrid, Spain, in 1941, 16 to 18 per cent of 561 persons had low hemoglobin (table 10).

Accordingly, Jolliffe, McLester and Sherman¹⁶² state that combining such data indicates "anemia in from 1.5 to 85 per cent of children, 3.6 to 30 per cent of adults and 9 to 72 per cent in pregnancy." Obviously the wide range of these estimates indicates that they are not particularly informative of the actual occurrence of nutritional anemia in the world population.

Such diverse and yet limited information affords too spotty a view of the character and scope of the problem of nutritional anemia to constitute a basis for sound public health practice. Nevertheless it is clear that where the condition has been searched for many cases have been found. In all probability nutritional anemia is of widespread, worldwide occurrence, and further extensive observations should be carried out in order to set up suitable public health and dietary practices to prevent this condition.

THE PROBLEM OF ADEQUATE NUTRITION

International attention was first given to nutrition and health by the League of Nations beginning in 1925 and culminating in the reports of the Technical Commission on Nutrition¹⁶⁵ and the Mixed Committee on Nutrition in 1937.¹⁶⁶ It is obvious that as measured by any modern standard of adequate nutrition much of the world's population is subsisting on inadequate food. In terms of adequate food for every one, no food surplus has ever existed. In terms of dietary adequacy the world has never had enough to eat. So-called overproduction and apparent surpluses have in reality been failures to secure adequate distribution. The recent United Nations Conference on Food and Agriculture¹⁶⁷ recognized that national and international

165. *Physiological Bases of Nutrition*, League of Nations Publications: II. Economic and Financial, 1936, II, B 4.

166. *Interim Report of the Mixed Committee on the Problem of Nutrition*, League of Nations Publications: II. Economic and Financial, 1936, II, B 3.

167. *United Nations Conference on Food and Agriculture: Final Act and Section Reports*, Dept. of State Publication 1948, Conference Series 52, 1943. Parran, Thomas: *A Blueprint for the Conquest of Hunger*, Pub. Health Rep. 58: 893 (June 11) 1943. Editorial, *Am. J. Pub. Health*. 33: 847, 1943.

agricultural policies must be directed toward obtaining a food supply adequate for health.

Although poverty is the principal cause of malnutrition, general economic improvement will not give every one an adequate diet. Faulty food distribution is the most important contributory factor, and ignorance of the rules of good diet plus indifference to the consequences and bad dietary habits are the contributory underlying causes.

Great Britain has shown that a national food policy based on nutritional adequacy can control malnutrition. Close control of food production, importation and prices together with strict rationing and with a food distribution system planned with the assistance of nutrition experts with the goal of adequacy instead of profit has assured an individual availability of foods with the result that, in spite of poorer living conditions incident to the war, the infant mortality in 1942 was the lowest on record and health has been maintained at a high level with a decreased general death rate and a negligible incidence of deficiency diseases.

From the point of view of preventive medicine the problem of adequate nutrition is so different from other health problems that it requires a new approach. Its ramifications extend far into our whole economic structure. Such diverse problems as the control of crop production, farm machinery, manpower, food distribution, transportation, food preservation and processing, storage and food preparation as well as nutrition education and the diagnosis, prevention and treatment of deficiency diseases are all involved. It is obvious that problems of this range and magnitude cannot be solved by physicians, health officers or any other one agency alone. The first essential is close cooperation and intimate relations among a number of agencies, including physicians and health officers.

A number of official and voluntary agencies in this country have been working on certain aspects of our nutrition problem for many years with little participation by physicians except from some health officers. The home economics and agriculture teachers in our high schools and colleges, the Agricultural Extension Service, the American Red Cross, the Children's Bureau

TABLE 10.—Nutritional Anemia

Location and Date	Number of Persons Studied	Age	Sex	Mean Hemoglobin		Mean R. B. C.		Per Cent Deficient	Standard Hemo- globin	References
				Entire Group	Hemo- globin	Entire Group	R. B. C., Millions			
Rural Pennsylv- ania and small Pennsylvania city 1939	898	All	♂ and ♀	41.24	4.76 or +	Mack, P. B.; Smith, J. M.; Logan, C. H.; Stewart, A. H., and Dodds, Paul: Richards Institute Pub. 2, part I, December 1942
Pennsylvania metropolitan school 1939	1,392	School age	709 ♀ 653 ♂	23.03 46.05 29.44	13.0 Gm. + 12.99-11.50 11.49-10.00	47.07 43.49 17.03	4.76 or + 4.75-4.51 4.50-4.26	Mack, P. B.; Smith, J. M.; Logan, C. H., and O'Brien, A. T.: Milbank Quart. 19, No. 3, 1941
Pennsylvania 1939	2,400	Preschool	♂ and ♀	9.03	4.25-4.01	51 ♂ 36 ♀	>11.5 Gm.	
		School	3.38	4.00 or -	19 ♂ 30 ♀	10-11.5 Gm.	
North Carolina town of 400 1940	?	Adult	±35 ♂ ±50 ♀	10-11.5 Gm.	Milam ¹⁵⁶
Oklahoma City 1939	1,000 pregnant women last tri- mester	Adult	♀	38.0 39.1 22.2 0.7	10.2-11.9 11.9-13.6 13.6-15.3 15.3+	16.4 4.71 29.2 4.6	3.0-3.5 3.5-4.0 4.0-4.5 4.5-5.0	Esbridge, J. B., and Serwer, M. J.: South. Med. J. 32: 24, 1939
Gainesville, Fla. 1939	620	School age	♂ and ♀	2.0 12.2 23.5	91-100% 81-90% 71-80%	5.0+	13.7 Gm. or 100%*	Abbott, O. D., and Ahman, C. F.: Am. J. Dis. Child. 55: 811, 1939
				15.6 13.5	51-60% 21-50%	9.6 Gm. or 70%† 11.7 Gm. or 85%‡	

	263	Preschool	♂ and ♀	3.4 23.1 40.0 14.4 7.2 4.8	91-100% 81-90% 71-80% 61-70% 51-60% 21-50%	13.7 Gm. or 100%* 9.6 Gm. or 70%† 11.7 Gm. or 85%‡	
New York City 1941	175 161 241 184	High school High income Low income	♂ ♀ ♂ ♀	0 3.1 2.5 4.3	Wiehl and Kruse *
New York State 1940	100	Adults	♂ and ♀	23	10.2 Gm. per 100 cc.	Scott, J. R., and Janeway, M. M.: New York State J. Med. 40: 440, 1940
New York City 1940	...	Adults	♂ ♀	7.6 6.8	♂ 14 Gm. ♀ 12 Gm.	N. R. C. Series No. 110, April 1942
Madrid, Spain 1941	561	All ages	♂ ♀ ♂ ♀	16 18 31 33	12 Gm. per 100 cc §	Robinson, W. D.; Janney, J. H., and Grande (Covian) Francisco: J. Nutrition 24: 557, 1942
Scotland 1933	?	Children Adolescent Adult	♂ and ♀ ♀ ♀	32 16 45	Davidson, L. S. P.: Fullerton, H. W.; Howie, J. W.; Croll, J. M.; Orr, J. B., and Godden, W.: Brit. M. J. 1: 685, 1933
Boston 1939	?	Adult	♀	16	Heath, C. W.: Symposium on the Blood and Blood Forming Or- gans, Wisconsin Press, 1939
Michigan 1939.	158	Adult (pregnant)	♀	26.6	10 Gm. per 100 cc.	Bethall, F. H.; Gardner, S. H., and MacKinnon, Frances: Ann. Int. Med. 13: 91, 1939
New York City 1939	325	Adult (pregnant)	♀	72	11.6 Gm. per 100 cc.	Labate, J. S.: Am. J. Obst. & Gynec. 38: 48, 1939
Kentucky 1940	?	Adult (pregnant)	♀	30 to 60	Gordon, Harold: Kentucky M. J. 38: 415, 1940

* Normal. † Anemic. ‡ Subnormal. § Standard red blood cells, 4,120,000.

of the Department of Labor and numerous other organizations have had continuing programs for a long time.

Many of our state health departments have established and maintained a small nutrition service at the state level with the assistance of the Children's Bureau. The attention here during peacetime was focused primarily on problems of maternal and child health, and an excellent start has been made. However, there are other population groups which also may be regarded as especially vulnerable from a nutritional point of view and to whom it is essential that attention also be given especially in wartime, for example school children, adolescents and workers in essential industries. In order to deal more effectively with these varied problems the regular nutrition activities of various government and voluntary agencies have been intensified, expanded and coordinated. A first meeting of representatives of these agencies was held in 1940, and in May 1941 President Roosevelt called the First National Nutritional Conference in Washington.¹⁶⁸

The National Nutrition Program was based on the recommendations of this conference, and coordination was obtained through the Nutrition Division of the Office of Defense Health and Welfare Services. These activities have now been incorporated into the Nutrition and Food Conservation Branch of the War Food Administration.

Regional nutritionists carry out the functions of this branch from the Food Distribution Administrative regional offices. On invitation these nutritionists work with state and local nutrition committees in planning and developing nutrition programs and projects. The most important accomplishment of this office has been the successful coordination of the nutrition program of various agencies, recognizing the place of each but centering attention on the common objective. It has shown that a coordinated program of this magnitude can be made to work in this country.

Nutrition committees have been formed in every state and in Hawaii and also are working on local nutrition problems in many counties, cities and local communities. In many instances there has been little or no

¹⁶⁸ Proceedings of the National Nutrition Conference for Defense. U. S. Govt. Printing Office, 1942.

participation by physicians or health officers in spite of invitations to medical societies and health departments to send representatives. The work of these committees has consisted mainly in the organization of nutrition classes, preparation and distribution of educational material, food demonstrations, victory gardens and home food preservation, and it is expected that they will play an increasingly important role in war food programs through school lunch activities and nutrition in industry subcommittees. If properly developed they should become the local body through which all the food and nutrition problems of the community are attacked.

The ultimate purpose of a civilian wartime food program is to assure "enough to eat" to every one, so that the war may be fought with the utmost efficiency. The phrase "enough to eat" in its proper use must mean not only enough in quantity but also enough of all essential dietary elements. This means that the entire program must be planned on a sound technical nutritional basis with adequate control of distribution together with price control of those constituents of the nation's food supply necessary to secure dietary adequacy.

Failure to recognize the necessity for basing the control on nutritional adequacy, or half-way measures of control, defeat the whole purpose of the program and are worse than no control in that they create a false sense of dietary security, and a ration coupon becomes a symbol of unobtainable food rather than a guaranty of a fair share of an item necessary for the maintenance of health.

It is also essential that any such program take into account the greater physiologic needs of the "vulnerable groups" in the population, among the most important of these groups during war being the workers in war industries. Differential rationing by allotting more ration coupons to such groups would threaten the whole rationing structure because of difficulties in administration and the great difficulty in assessing the actual needs of the individual based on his special requirements. In general the most practicable solution is to develop feeding facilities within each industrial plant which can supply an adequate midshift meal to every

employee without requiring ration coupons. In a few industries operating under special conditions of isolation from the usual food supply, it may be necessary to supply extra food to the entire establishment. Here the allocation is made to the group and not to the individual. Rare exceptions, such as sheep herders, may require special allocations.

The aspect of industrial nutrition which involves the community can be attacked by the local nutrition committee. Inplant feeding should be regarded as one aspect of a properly developed industrial hygiene program. It should be approached through the plant medical officer or safety director after the plant management has agreed to the program.

At the federal level the War Food Administration works closely with the Industrial Hygiene Division of the National Institute of Health of the United States Public Health Service. At the state level, when state health departments have industrial hygiene officers they should be one of the points of contact with the plant, using the advice and assistance of the local and state nutrition committee. Because of the scope and importance of the industrial nutrition problem the War Food Administration has appointed regional nutrition representatives to work with state and local committees as well as health officers and plant officials.

On request from industrial plants, industrial nutritionists assist in planning employee feeding and nutrition education programs and in handling applications for essential equipment and food. They also work with labor groups in promoting better eating habits.

In many states industrial nutrition subcommittees have been organized under the state nutrition committee. The representative of the health department should work with these subcommittees, which include industrial physicians, caterers, representatives of labor, plant management and other interested groups.

Nutrition committees throughout the country are constantly striving to improve the public knowledge of nutrition and to develop better food habits. Food shortages make these activities more important than ever. This education is based on food groups designed to yield nutritional adequacy with considerable latitude in the choice of food items. The recommendation is

a type diet which for application requires local adaptation to specific items. The necessary foods are listed in seven groups (table 11).

Physicians and health officers should assist in the promotion of sound nutrition education as well as in promoting good food programs designed to improve nutrition. The health officer has both an opportunity and an obligation here in preventive medicine which cannot be performed as well by any other group. The concept of the prevention of disease must be enlarged to include an effort to attain the best possible level of

TABLE 11.—*Necessary Foods*

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|--|
| 1. Green and yellow vegetables, some raw, some cooked, frozen or canned. |
| 2. Oranges, tomatoes, grapefruit or raw cabbage or salad greens. |
| 3. Potatoes and other vegetables and fruits raw, dried, cooked, frozen or canned. |
| 4. Milk and milk products, fluid, evaporated, dried milk or cheese. |
| 5. Meat, poultry, fish or eggs or dried beans, peas, nuts or peanut butter. |
| 6. Bread, flour and cereals, whole grain or enriched or restored. |
| 7. Butter and fortified margarine (with added vitamin A). "Eat some food from each group every day." |
| "In addition to the basic 7, eat any other foods you want." |
-

Further instructions in order to cover possible wartime shortages are as follows:

<i>If scarce in</i>	<i>Use more from</i>
Group 2	Group 1, 3
Group 4	Group 1, 5, 6
Group 5 (meats)	Group 4, 5 (eggs)
Group 7	Group 1, 4

health which is unknown in the absence of good nutrition.

The fact that malnutrition and deficiency diseases usually appear insignificant in mortality and morbidity tables does not reflect the real importance of nutrition in our national health. Although good nutrition does not guarantee good health, poor nutrition can and often does contribute to mortality from other primary causes, while optimum nutrition can contribute to optimum health.

The health officer and physician can help determine the prevalence of malnutrition and relate nutrition problems to other public health and medical problems. Some of the more important activities for health departments

in developing this field in collaborating with existing programs were recently proposed by Sebrell and Wilkins¹⁶⁹ as follows:

STATE HEALTH DEPARTMENT ACTIVITIES

1. Collect information and do appraisals on the incidence and types of deficiency diseases and on food habits in geographical areas and population groups, especially children, pregnant and lactating women and industrial workers. Even small samplings are of value in pointing the way to more comprehensive appraisals.

2. Offer assistance in the diagnosis of nutritional deficiencies. Here is a health department service which is in line with sound public health principles and which will strengthen the work of other agencies in this field. At the same time the efforts of other agencies will contribute greatly to creating a demand for this type of service.

3. Prepare and distribute simple attractive literature dealing with state nutrition problems. Such literature should be prepared with a full knowledge of all other nutrition literature being used by other agencies in order that duplication and conflicting viewpoints may be avoided.

4. Cooperate actively with other agencies dealing with different aspects of the nutrition problem. Offer the specialized services of the health department to other agencies to help them in dealing with their particular phases of nutrition.

5. Take an active part in the work of the state nutrition committee.

6. Offer information, consultation, guidance and encouragement to local health departments in developing local nutrition programs and in cooperating with the local nutrition committees.

7. Promote staff education in nutrition, including facilities for professional education in public health nutrition, and education of county and city health department personnel in nutrition activities.

8. Assist in sponsoring conferences and refresher courses in nutrition and related fields for public health and school personnel. During the past three summers nine such cooperatively sponsored six week conferences have been held in one state. Similar projects have been successfully carried out in several other states.

9. Active participation of nutritionists in the public health nursing and dental hygiene program, in well child clinics, in school health programs and in other activities of the maternal and child health division.

169. Sebrell, W. H., and Wilkins, Walter: *The Role of the Health Department in the National Nutrition Program*, Pub. Health Rep. 58: 805 (May 21) 1943.

10. Include nutrition in the industrial hygiene program not only by nutrition education in the plant, but also by improving plant feeding facilities and the nutritional quality of the meals served.

11. Cooperate with and assist the state food distribution administrator in locating and meeting local food problems.

12. Take an interest in school lunch programs. The United States Public Health Service can consider requests for nutritionists for these programs under title VI funds if recommended and requested through local and state health departments. Under rationing we should give more attention than ever to the adequacy of the meals our children get at school.

LOCAL HEALTH DEPARTMENT ACTIVITIES

1. Learn what other agencies have done and are doing within the area.

2. Affiliate with the local nutrition committee.

3. Study the nutritional status and needs of the area from medical and public health angles and help orient other agencies in this regard.

4. Distribute and interpret nutrition teaching material, especially material which deals primarily with local problems.

5. Have a planned program for staff education in nutrition within the department or in cooperation with other agencies.

6. Exert a stabilizing influence and interpret sound nutrition practices to the public, avoiding fads and extremes.

7. Interpret local nutritional conditions to the public through talks, newspaper articles, radio programs and so on.

8. Make an effort to increase the interest of local medical and dental professions in local nutrition problems and practical solutions.

9. Develop nutrition educational facilities for patients who attend public health clinics. In some places it may be advisable to establish clinics to deal primarily with nutrition problems.

10. Develop and maintain a movie, film strip, and slide library on nutrition and related subjects.

11. Encourage public eating places to serve food of good nutritional value and to prepare their foods in such a way as to conserve vitamins and minerals. This might be started as a consultation service.

12. Encourage civic clubs to sponsor programs which, either directly or indirectly, will improve the nutrition status of groups within the community.

13. Advise and sponsor feeding facilities in connection with child day care programs.

14. Stress nutrition in school health programs:

(a) Cooperate with teachers, parent-teachers associations and lunchroom managers in improving school lunches.

(b) Sponsor cooperative school lunch programs.

(c) Encourage the use of simple, wholesome, home prepared foods in lunchboxes rather than the use of "store bought" snacks.

(d) Watch for and stress nutritional deficiencies in physical examination of school and preschool children.

(e) When practical, conduct or sponsor demonstrations with school children showing results of improved nutrition (properly integrated with other health habits).

(f) Sponsor "sampling surveys" of school children for nutritional status. If possible, get local medical and dental societies to cooperate.

From a national point of view the state of nutrition of a considerable part of the population of this country is unsatisfactory and has been so for many years. Whether even this present state of nutrition can be maintained in the face of the present food situation depends on the efficiency with which we produce, distribute and utilize our food supplies. The signs and symptoms of malnutrition are often overlooked or attributed to other causes. Gross deficiency disease still exists, and the relationship of nutrition to other health problems is not common knowledge as it should be. Poor methods of using, preserving and preparing foods both in homes and in public eating places are responsible for tremendous losses in food values. Even in the face of food shortages there is as yet little tendency to conserve and use every bit of edible food. The uses of alternate foods when shortages exist is little appreciated. A shortage in beef results in a public clamor to satisfy the palate although physiologic needs can be met easily from other food sources without difficulty.

There is probably more public interest in nutrition and food today than ever before. Physicians and health officers can play an enormously important part in the national effort to improve nutrition by guiding this interest along sound lines. Too often the busy physician finds it easier to prescribe a vitamin pill than to investigate food habits and recommend dietary changes. Health officers need to become acquainted with the nutrition work being done by other agencies and have their staff members take their proper place in the nutrition program after they have obtained a background of knowledge of the work being done by other organizations.

We have an unparalleled opportunity in the field of preventive medicine. If agriculture is to be based on

the nutritional needs of the population, health and medical authorities should determine what those needs are. Satisfactory nutrition depends on health and agricultural authorities working together. Agriculture up to now has had to assume the major portion of the burden of solving our nutritional problems. It is past time for medical and health authorities to assume their share of the responsibility.

CHAPTER XXIV

CONDITIONED MALNUTRITION

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The terms "malnutrition," "nutritional deficiency disease," "nutritional failure," "beriberi," "pellagra," "scurvy," "riboflavin deficiency" and similar terms signify to many persons disorders arising solely from an inadequate diet. But all these may occur in the presence of dietary adequacy. As pointed out by Kruse,¹ these terms should denote a deficiency in the bodily tissues rather than in the diet. If a tissue deficiency arises from an inadequate diet it is known as a primary deficiency. If the tissue deficiency is caused by factors other than an inadequate diet alone it is known as a conditioned or secondary deficiency. Conditioned deficiencies are caused by factors that interfere with the ingestion, absorption or utilization of essential nutrients, or by factors that increase their requirement, destruction or excretion.²

The importance of these conditioning factors as a cause of deficiency disease has not been generally recognized. In surveys of the nutritional status of population groups there has been a tendency to neglect the causal role of these conditioning factors and attribute all malnutrition to dietary inadequacies alone. On the other hand, in hospital and office practice the finding of clearcut gross manifestations of deficiency disease caused by conditioning factors may lead to one of the following two errors: The first is to consider the lesion a manifestation of the original or conditioning disease unrelated to tissue nutritional deficiency. The second, after recognizing the nutritional basis of the secondary manifestation, is to ascribe the original or conditioning disease to nutritional deficiency. Those making the first error ignore the existence of deficiency disease,

1. Kruse, H. D.: A Concept of Malnutrition, *Milbank Mem. Fund Quart.* 30: 245 (July) 1942.

2. Jolliffe, Norman: Chapter on Nutrition and Deficiency Diseases in *Preventive Medicine in Modern Practice*, New York, Paul B. Hoeber, 1942.

while those making the second error attribute most deviations from normal health to malnutrition.

The prevention and treatment of these conditioned deficiency diseases are often the decisive factors in determining recovery after surgery³ and in many severe infections. Likewise their prevention and treatment often decide the success of other therapeutic measures directed toward alleviating the conditioning disease. In addition, the comfort, length of life and economic usefulness of many patients depend on adequate nutrition.⁴

THE POSSIBLE NONSPECIFICITY OF CERTAIN LESIONS OF MALNUTRITION

The gross evidence (table 1) and the better established special examinations (table 2) for the detection of malnutrition as outlined by Jolliffe, McLester and Sherman⁵ are listed in the accompanying tables. Since these manifestations, whether primary or conditioned, are identical, it is not necessary to redescribe them here. It is necessary to point out, however, that with few exceptions the findings characteristic of malnutrition are nonspecific. Some lesions attributable to malnutrition may be produced by local tissue deficiency⁶ as a result of circulatory disturbances, trauma pressure or infection. These local conditioning factors may produce lesions identical with those of a systemic deficiency. Other lesions may not be related to either systemic or local tissue deficiency but may be due to some factor other than malnutrition. These facts indicate that all the diagnostic skill and clinical acumen employed by physicians in any other branch of clinical medicine must be employed in the interpretation of

3. Brown, P. B., and Donald, C. J., Jr.: Prognosis of Regional Enteritis, *Am. J. Digest. Dis.* **9**: 87 (March) 1942. Starr, Paul: Value of Vitamins in Surgical Practice: Collective Review, *Internat. Abstr. Surg.* **74**: 309, in *Surg., Gynec. & Obst.*, April 1942. Hartzell, J. B., and Crowley, R. T.: Vitamin Therapy in the Surgical Patient, *Am. J. Surg.* **56**: 288 (April) 1942. Pollack, Herbert; Ellenburg, Max, and Dolger, Henry: Postoperative Precipitation of Vitamin B Complex Deficiencies, *J. Mount Sinai Hosp.* **8**: 925 (Jan.-Feb.) 1942.

4. Jolliffe, Norman: Treatment of Neuropsychiatric Disorders with Vitamins, *J. A. M. A.* **117**: 1496 (Nov. 1) 1941.

5. Jolliffe, Norman; McLester, J. S., and Sherman, H. C.: The Prevalence of Malnutrition, *J. A. M. A.* **118**: 944 (March 21) 1942.

6. McCullough, Kendrick, and Dalldorf, Gilbert: Epithelial Metaplasia: Experimental Study, *Arch. Path.* **34**: 486 (Oct.) 1937. Dalldorf, Gilbert: The Pathological Responses to Vitamin Deficiencies, *Bull. New York Acad. Med.* **14**: 635 (Oct.) 1938. Straumfjord, J. V.: Lesions of Vitamin A Deficiency: Their Local Character and Chronicity, *Northwest Med.* **41**: 229 (July) 1942.

lesions usually ascribed to malnutrition. The following observations illustrate this point:

Xerosis conjunctivae is a lesion characteristic of vitamin A deficiency in animals⁷ and one that responds to massive vitamin A therapy in man.⁸ From this it should not be inferred that all "spots" or elevations

TABLE 1.—*Gross Evidences of Malnutrition*

System	Finding	Suggested Deficiency or Syndrome
Eyes	Xerosis conjunctivae and corneae.....	Vitamin A
	Central ophthalmoplegia	Thiamine
Mucous membranes	Scarlet red stomatitis and glossitis with or without secondary Vincent's infection	Nicotinic acid
	Magenta glossitis ..	Riboflavin
	Atrophic glossitis	Nicotinic acid, B complex, addisonian anemia, Plummer-Vincent syndrome
	Scorbutic gums	Ascorbic acid
	Cheliosis	Riboflavin
	Nonspecific urethritis, balanitis, vaginitis	Nicotinic acid
Skin	Pellagrous dermatitis	Nicotinic acid
	Seborrheic lesions in nasolabial folds on face, behind ears and in skin folds	Riboflavin
	Hyperkeratosis and hyperfolliculosis..	Vitamin A
	Hemorrhagic manifestations	Vitamin K, ascorbic acid
	Fissures in angles of mouth.....	Riboflavin
Neurologic	Characteristic bilateral symmetrical polyneuropathy	Thiamine
	Combined system syndromes.....	Thiamine, B complex, addisonian anemia
	Wernicke's syndrome	Thiamine, B complex
	Nicotinic acid deficiency encephalopathy	Nicotinic acid
	Progressive stupor and hebétude.....	Nicotinic acid
	Certain organic reaction psychoses. .	Nicotinic acid, thiamine and B complex
Skeletal	Rachitic deformities and osteomalacia	Vitamin D, calcium, phosphorus
General	Underweight, underheight, edema, pallor	Calories, proteins, iron, B complex

that appear on the eyeballs peripheral to the cornea are xerosis conjunctivae. Some are, but others are pterygium and others scleral deposits of varying com-

7. Bessey, O. A., and Wolbach, S. B.: Vascularity of the Cornea of the Rat in Riboflavin Deficiency, with a Note on Corneal Vascularization in Vitamin A Deficiency, *J. Exper. Med.* **69**:1 (Jan.) 1939; Vitamin A. Physiology and Pathology, J. A. M. A. **110**:2072 (June 18) 1938; Wolbach, S. W.: The Pathologic Changes Resulting from Vitamin Deficiency, *ibid.* **108**:7 (Jan. 2) 1937.

8. Kruse, H. D.: Medical Evaluation of Nutritional Status: IV. The Ocular Manifestations of Avitaminosis A, with Especial Consideration of the Detection of Early Changes by Biomicroscopy, *Pub. Health Rep.* **56**:1301 (July 27) 1941; *Milbank Mem. Fund Quart.* **19**:207 (July) 1941.

position. The contention of Kruse⁸ that xerosis conjunctivae is a manifestation of chronic vitamin A deficiency has been criticized by Berliner,⁹ who points out that not all the photographs published by Kruse⁸ were characteristic of xerosis conjunctivae, that the vitamin A blood levels are not low, and that many of the lesions in question are those usually ascribed to simple senile changes. It should be noted, however, that trained ophthalmologists after gross and slit lamp examinations frequently disagree on the appropriate anatomic labeling in a high proportion of "spot" cases. The blood level of vitamins does not necessarily reflect the state of the tissues and cannot be used as a criterion for the absence of a deficiency disease, particularly a chronic deficiency anatomically manifest.¹⁰ In this type of malnutrition the blood reflects the recent intake of vitamin A. Also to designate lesions of the conjunctiva as senile changes with the implication that senility per se is responsible for them is unsatisfactory. This merely identifies the condition with a population in which it is frequently found but does not explain its cause. Even in arteriosclerosis, age is not the essential cause. As William Boyd¹¹ has stated, "The advance in years merely permits some slowly acting cause to produce the effects in the vessels." In discussing the lesions of chronic malnutrition, Kruse¹ states that "not all elderly persons show the changes. On the other hand they occur in children. Time, not senility, is the essential point, and time does not start the changes, it is simply a dimension over which they progress. They are specific avitaminoses in a state of chronicity, due usually to respective dietary deficiencies running over a period of years. Their prevalence and severity vary with the number and degree of deficient diets. . . . Most important of all, they are reversible, yielding slowly but completely to appropriate therapy." This latter point has been partially confirmed by Jolliffe and Stern,¹² who observed that, of

9. Berliner, M. L.: Regarding Early Detection of Avitaminosis A by Gross or Biomicroscopic Examination of Conjunctiva, *Am. J. Ophthalm* 25: 302 (March) 1942.

10. Patek, A. J., Jr., and Haig, Charles: Effect of Administration of Thyroid Extract and of Alpha-Dinitrophenol on Dark Adaptation, *Proc. Soc. Exper. Biol. & Med.* 46: 180 (Jan.) 1941.

11. Boyd, William, quoted by Piersol, G. M.: Arteriosclerosis: Social Significance and Recent Advances in Treatment, *Bull. New York Acad. Med.* 18: 36 (Jan.) 1942.

12. Jolliffe, Norman, and Stern, Marvin: Objective Manifestations of Nutritional Deficiency Diseases, *Clinics* 1: 282 (Aug.) 1942.

10 subjects given 50,000 units of vitamin A twice daily by mouth for ten months, 7 showed definite evidence of responding in the manner described by Kruse. It seems, therefore, that some of these lesions respond to vitamin A therapy. Some may not, but sufficient time has not yet elapsed to decide this point definitely. Complete solution of this problem requires further study, especially the biomicroscopic slit lamp examination of the conjunctivas of experimental subjects maintained with diets deficient in vitamin A.

Corneal vascularity is undoubtedly associated with riboflavin deficiency in many subjects.¹³ In acute cases

TABLE 2.—*Special Examinations for Detection of Malnutrition*

Examination	Condition It May Detect
Roentgenogram of hand and wrist, elbow and hip	Rickets and scurvy in children; osteomalacia and scurvy in adults
Roentgenogram of heart....	Advanced beriberi
Electrocardiogram.....	Changes suggestive of thiamine deficiency
Biomicroscopic eye examination with slit lamp	Capillary invasion of cornea (riboflavin deficiency); changes in conjunctivas (vitamin A deficiency)
Red blood cell count....	Iron deficiency anemia; Addisonian anemia; macrocytic anemia
Hemoglobin.....	
Stained blood smear...	
Red blood cell volume..	Vitamin C undersaturation
Plasma ascorbic acid...	
Serum calcium.....	Vitamin D deficiency
Serum phosphatase..	
Serum phosphorus....	Vitamin B ₁ deficiency
Blood pyruvic acid..	
Serum protein or albumin	Protein deficiency
Blood prothrombin.....	Vitamin K deficiency

this condition can be observed by slit lamp biomicroscopy to disappear following riboflavin administration, to return when riboflavin is withheld and to disappear again when treatment is resumed. In this acute type of lesion the ocular symptoms of burning, itching, asthenopia, photophobia and lacrimation are extremely common. Some investigators¹⁴ have used corneal vas-

13. Sydenstricker, V. P.; Sebrell, W. H.; Cleckley, H. M., and Kruse, H. D.: The Ocular Manifestations of Ariboflavinosis, *J. A. M. A.* **114**: 2437 (June 22) 1940. Johnson, L. V., and Eckhardt, R. E.: Rosacea Keratitis and Conditions with Vascularization of Cornea Treated with Riboflavin, *Arch. Ophth.* **23**: 899 (May) 1940. Sydenstricker, V. P.; Kelly, A. R., and Weaver, J. W.: Ariboflavinosis with Special Reference to the Ocular Manifestations, *South. M. J.* **34**: 165 (Feb.) 1941.

14. Kruse, H. D.; Palmer, C. E.; Schmidt, W., and Wiehl, Dorothy C.: Medical Evaluation of Nutritional Status: I. Methods Used in a Survey of High School Students, *Milbank Mem. Fund Quart.* **18**: 257 (July) 1940. Wiehl, Dorothy G., and Kruse, H. D.: Medical Evaluation of Nutritional Status: V. Prevalence of Deficiency Diseases in Their Sub-clinical Stages, *ibid.* **18**: 241 (July) 1941.

cularity as an index of riboflavin deficiency in surveys of population groups. Several observers¹⁵ have warned, however, that it is not yet confirmed that all or nearly all of these vascular changes are due only to riboflavin deficiency or that they are a necessary accompaniment of other undoubted signs of riboflavin deficiency. Youmans and Patton¹⁶ have observed a considerable number of subjects with mild but definite corneal vascularization not accompanied by ocular symptoms and in whom there was no correlation with dietary intake of riboflavin, other dietary factors or other evidence of deficiency disease. Reexamination of these subjects showed an improvement or disappearance of the vascularization in the winter or spring season compared with the fall, in spite of a lower intake of riboflavin in the former period. This study suggests that factors other than riboflavin are concerned. Youmans and Patton¹⁶ say "there is some evidence to suggest that such a factor (there may be others) is light, . . . which may be concerned in the production of a vascularization through the mechanism of a local deficiency without any general deficiency being present. In general, the conclusion which seems indicated is that corneal vascularization, even of the characteristic type and of definite degree, does not always mean a general riboflavin deficiency." Youmans and Patton¹⁶ then point out that under these circumstances the lesion loses some of its value as a diagnostic test of riboflavin deficiency in population groups. For clinical purposes, however, this finding is not only the most helpful and reliable but the simplest and quickest means of detecting mild riboflavin deficiency. To distinguish it from those instances of vascularization which seem to be caused by other agencies, it is as a rule necessary only to consider with it the history, the findings of the physical examination and the results of a therapeutic trial.

15. Sebrell, W. H.: *Vitamins and Public Health*, Fed. Proc. 1:319 (Sept.) 1942. Jolliffe, Norman, and Goodhart, Robert: *Vitamins in the Practice of Medicine*, *ibid.* 1:316 (Sept.) 1942. Youmans, J. B.; Patton, E. W.; Robinson, W. D., and Kern, Ruth, M. S.: *An Analysis of Corneal Vascularity as Found in a Survey of Nutrition*, 57th annual meeting of Assn. of Am. Physicians, May 5, 1942. Mack, Pauline Berry, and Smith, Janice Minerva: *Methods of Conducting Mass Studies in Human Nutrition*, Pennsylvania State College Bull. 38, No. 43, 1939 (in revision).

16. Youmans, J. B., and Patton, E. W.: *The Laboratory Diagnosis of Nutritional Deficiencies*, Clinica 1:303 (Aug.) 1942.

The central bilateral ophthalmoplegia of Wernicke's syndrome is due to severe acute thiamine deficiency,¹⁷ but ophthalmoplegias occur from many other causes. Central ophthalmoplegias are common in central nervous system syphilis, multiple sclerosis, basilar meningitis, diphtheritic neuritis and encephalitis.¹⁸ A characteristic bilateral symmetrical polyneuropathy occurs in chronic thiamine deficiency, but a clinically similar polyneuropathy may be due to infectious polyneuritis of the Guillain-Barré type¹⁹ to various intoxicants, to heavy metal poisonings¹⁸ or even to deficiencies of vitamins other than thiamine.²⁰

The mucous membrane lesions in and about the mouth²¹ present complex diagnostic problems. Some cases showing a magenta glossitis respond to riboflavin,²² some to pyridoxine²³ and others only to crude liver extract administered parenterally. Cheilosis may appear the same whether due to ariboflavinosis, to edentulous mouth,²⁴ to allergy or to lipstick. Scarlet fungiform papillae at the tip of the tongue are the earliest visible signs of mild acute nicotinic acid deficiency,²⁵ but pipe smoking, particularly in persons unaccustomed to a pipe, may produce a similar picture. Vincent's gingivitis and stomatitis may occur in deficiencies of both ascorbic acid and nicotinic acid.¹² This

17. Jolliffe, Norman; Wortis, Herman, and Fein, H. D.: The Wernicke Syndrome, *Arch. Neurol. & Psychiat.* **46**: 569 (Oct.) 1941. Wortis, Herman, and Jolliffe, Norman: The Present Status of Vitamins in Nervous Health and Disease, *New York State J. Med.* **41**: 1461 (July 15) 1941. Alexander, Leo: Beriberi and Wernicke's Hemorrhagic Polioencephalitis, III Cong. Neurol. Internat., Comptes rend. des séances, Copenhagen, Aug. 21, 1939, p. 913.

18. Wechsler, I. S.: *A Textbook of Clinical Neurology*, Philadelphia and London, W. B. Saunders Company, 1939.

19. De Sanctis, A. G., and Greene, Martin: Acute Infectious Polyneuritis: A Diagnostic Problem During a Poliomyelitis Epidemic, *J. A. M. A.* **118**: 1445 (April 25) 1942.

20. Wintrobe, M. M.; Miller, M. H., and Falles, R. H., Jr.: What is the Antineuritic Vitamin? Read at the 57th annual meeting of the Association of American Physicians, May 5, 1942.

21. Jeghers, Harold: Nutrition: The Appearance of the Tongue as an Index of Nutritional Deficiencies, *New England J. Med.* **227**: 221 (Aug. 6) 1942. Martin, Hayes, and Koop, C. E.: The Precancerous Mouth Lesions of Avitaminosis B; Their Etiology, Response to Therapy and Relationship to Intraoral Cancer, *Am. J. Surg.* **57**: 195 (Aug.) 1942.

22. Sydenstricker, V. P.: Clinical Manifestations of Nicotinic Acid and Riboflavin Deficiency (Pellagra), *Ann. Int. Med.* **14**: 1499 (March) 1941.

23. Ruffin, J. M., and Smith, D. T.: Pellagra Therapy, *Tr. Am. Clin. Otol. A.* (1939) **55**: 192, 1940.

24. Ellenberg, Max, and Pollack, Herbert: Pseudoariboflavinosis, *J. A. M. A.* **119**: 790 (July 4) 1942.

25. Kruse, H. D.: The Lingual Manifestations of Aniacinosis, with Especial Consideration of the Detection of Early Changes by Biomicroscopy, *Milbank Mem. Fund Quart.* **20**: 262 (July) 1942. Jeghers,²¹ Martin and Koop.²¹

infection becomes active only in the presence of necrotic tissue. Ascorbic acid and nicotinic acid deficiencies are only two of many causes of tissue necrosis in the mouth.

CONDITIONING FACTORS

Following the definition of a conditioned deficiency disease given at the beginning of this paper, the various illnesses and conditions that may produce such deficiencies are listed in tables 3 to 8. It must be emphasized that these tables are not complete but are intended merely to list the more common illnesses, therapeutic measures and physiologic alterations which condition the production of a deficiency syndrome.

Interference with Ingestion.—Strictly speaking, deficiency disease produced by interference with ingestion should not be considered conditioned. Since failure to ingest adequate amounts of food is alone responsible, it would be reasonable to consider these cases as primary deficiencies. Practically, however, in view of the frequency with which disease may interfere with adequate food intake and because of the significance of this classification for preventive therapy, its inclusion as a conditioning factor is warranted. The more common of these conditions are listed in table 3. Gastrointestinal and neuropsychiatric disorders, food allergy and nausea of pregnancy are noted for their interference with food intake, and the literature is replete with references to deficiency diseases developing under these conditions.²

In hospitals a meal placed at the patient's bedside is often considered, on the record at least, as eaten, while actually the patient may have consumed little or none of it. Although this may occur under many conditions, it is particularly likely to occur in elderly patients whose hospitalization is more custodial than therapeutic, who may be confused and whose dentures may be in the property room. Within one week 5 such patients with gross deficiency disease have been admitted to my service from "custodial" institutions. Jolliffe, Fein and Rosenblum²⁶ have recently reported an illustrative case of classic scurvy, pellagra and riboflavin deficiency in a person transferred from a custodial institution where she had been a patient for the previous five years.

26. Jolliffe, Norman; Fein, H. D., and Rosenblum, L. A.: Riboflavin Deficiency in Man, *New England J. Med.* **231**: 921 (Dec. 14) 1939.

Alcohol, though it also produces deficiency disease by other means,²⁷ may prevent an adequate food intake. It does this by replacing other food and by causing nausea and vomiting through its irritant action on the gastric mucosa. This may result in a thiamine deficiency causing anorexia, which in turn results in deficient intake of other nutrients. In this respect thiamine deficiency is frequently the underlying cause of other deficiencies. In some subjects the anorexia caused by lack of thiamine is a protective mechanism, guarding the subject against a high caloric intake. However, civilized man on developing anorexia limits his food intake as a rule not to smaller amounts of a balanced diet but to crackers, toast, tea, coffee, sugar and alcohol.

TABLE 3—*Factors Interfering with Ingestion*

1. Gastrointestinal disorders
Acute gastroenteritis, gallbladder disease, peptic ulcers, diarrheal diseases and obstructive lesions of gastrointestinal tract
2. Neuropsychiatric disorders
Neurasthenia, neurosis, psychoneurosis, psychoses, migraine and neurologic disorders interfering with self feeding
3. Anorexia
Alcohol, operations, anesthesia, infectious diseases, congestive heart failure, thiamine deficiency, visceral pain
4. Food allergy
5. Loss of teeth
6. Pregnancy
7. Therapy
Diets restricting ingestion of essential foods

With such a diet almost any of the deficiency diseases may develop.

Therapeutic measures often produce deficiency diseases by needlessly restricting the ingestion of certain essential nutritional factors. For example, diets prescribed for patients having allergy, peptic ulcers, biliary disease, nephritis, hypertension, colitis, diabetes or obesity are often deficient in one or more of the essential nutrients. Such diets may occasionally produce more serious disease than the original condition for which the diet was prescribed. Especially harmful are "slimming" diets published in newspapers. Fortunately their low caloric content gives some measure of protection for short periods of time, but, if persisted in, serious damage due to malnutrition may occur. The

27. Jolliffe, Norman: The Influence of Alcohol on the Adequacy of the B Vitamins in the American Diet, *Quart. J. Stud. on Alcohol* 1:74 (June) 1940.

physician should discourage such unbalanced diets, but if despite advice they are persisted in, a multivitamin preparation, preferably containing the full daily allowances recommended by the Food and Nutrition Board of the National Research Council,²⁸ should be prescribed. Even well planned reducing diets prescribed by the physician are likely to be short in the B vitamins. For this reason their supplementation with a satisfactory source of these vitamins is desirable. Dried brewers' yeast and extracts of brewers' yeast may be used for this purpose.

Increased Bodily Requirements.—Strictly speaking, malnutrition caused by failure to meet increased bodily requirements need not be considered as conditioned, since it is inadequate ingestion of food that is alone responsible. Practically, however, when the metabolic requirement is increased beyond the usual or average range it is warranted to consider this as a conditioning factor. Fever increases the basal metabolism by 7.2 per cent for each degree F.,²⁹ while strenuous physical exertion may increase it as much as fifteen times the basal level.²⁹ The requirement of many nutritive essentials parallels total metabolism whether the change in total metabolism is brought about by physical exertion, disease, environment or drugs. These conditions are listed in table 4.

The occurrence of deficiency diseases conditioned by fever, hyperthyroidism, pregnancy and lactation are well known. Less well recognized are the effects of abnormal physical activity and unusual environmental factors. Johnson and his collaborators³⁰ have recently demonstrated an increased requirement of the B vitamins conditioned by moderately strenuous physical activity common to farmers, soldiers and other workers. In a group of men subjected to physical labor equivalent to an output of 4,000 to 5,000 calories, definite deterioration in physical fitness occurred well within one week of starting labor with a diet deficient in the

28. Recommended Allowances for Various Dietary Essentials, Committee on Food and Nutrition, National Research Council, J. Am. Dietet. A. 17: 565 (June-July) 1941.

29. Duncan, G. G.: Diseases of Metabolism, Philadelphia, W. B. Saunders Company, 1942.

30. Johnson, R. E.; Darling, R. C.; Forbes, W. H.; Brouha, L.; Egafia, E., and Graybiel, A.: The Effects of a Diet Deficient in Part of the Vitamin B Complex on Men Doing Manual Labor, J. Nutrition 24: 585 (Dec.) 1942.

vitamin B complex. Such deterioration could be prevented or cured by the entire B complex containing only 0.6 mg. of thiamine daily but not by 2.0 mg. of thiamine hydrochloride alone. The applicability of these findings to workers in industry, to men in the armed forces and to patients having delirium or a psychosis with pronounced increase in psychomotor activity is obvious.

Sunlight has been recognized as a precipitating agent in pellagra since Gheradini³¹ in 1792 produced pellagrous skin lesions on various parts of the body by exposure to the sun. In fact this disease is known among the peasants in Italy as *mal del sole*. Since the recognition of pellagra in this country, many clinicians³²

TABLE 4.—*Factors Increasing Nutritive Requirement*

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- | | |
|----|--|
| 1. | Abnormal activity, as associated with
Prolonged strenuous physical exertion, delirium and certain psychoses |
| 2. | Abnormal environmental factors
Excessively high temperatures, as in the tropics, in deserts and in certain industries
Excessive light glare as from snow or klieg lights |
| 3. | Fever |
| 4. | Hyperthyroidism |
| 5. | Pregnancy and lactation |
| 6. | Therapy such as thyroid, alpha-dinitrophenol, parenteral dextrose solutions, fever therapy, high carbohydrate diets |
-

have called attention to the possible relationship between exposure to sunlight and the development of the skin lesions. Others³² have confirmed Gheradini's experiments and in addition have shown that the same exposure in normal subjects leads only to the development of a healthy tan. Furthermore, other trauma, such as radiant energy, dirt, filth and chemical trauma, is believed also to condition nicotinic acid deficient persons to the development of skin lesions.³³ Sunlight not only conditions nicotinic acid deficient persons to skin lesions but is thought by some³⁴ to play a role in conditioning riboflavin deficient persons to corneal vascularity. Johnson and Eckhardt¹³ have demonstrated the

31. Gheradini, quoted by Harris, Seale; *Clinical Pellagra*, St. Louis, C. V. Mosby Company, 1941.

32. Reviewed by Harris.³¹

33. Smith, D. T., and Ruffin, J. M.: *Effect of Sunlight on the Clinical Manifestations of Pellagra*, Arch. Int. Med. 59: 631 (April) 1937.

34. Kruse, H. D.: Personal communication to the author. Tisdall, F. F.: Personal communication to the author.

effect of sunlight in hastening the onset of corneal vascularization in riboflavin deficient rats, and Sydenstricker, Kelly and Weaver¹⁸ suggest the possibility that prolonged exposure to bright light may cause destruction of riboflavin in the cornea with the production of ocular signs in the absence of lesions elsewhere. Mechanical irritation has been shown to determine the localization of epithelial metaplasia in vitamin A deficiency,⁶ while ill fitting dentures and edentulousness which causes caving in of the angles of the mouth may condition the lips to cheilosis.²⁴

By increasing total metabolism, various therapies may produce a conditioned deficiency disease. Drugs such as dinitrophenol, thyroxin and thyroid¹⁰ and fever therapy³⁵ act by increasing metabolism, while parenteral administration of dextrose, insulin shock therapy and high carbohydrate diets act by increasing the requirement for coenzymes without an increase in total metabolism.³⁶ Many investigators believe that long continued parenteral administration of dextrose is dangerous to patients, particularly those in a borderline state of nutrition. The oxidation and decarboxylation of pyruvic acid, one of the intermediate products of carbohydrate metabolism, requires an enzyme-coenzyme system consisting of a specific protein enzyme (carboxylase), a cocarboxylase (thiamine-pyrophosphate) and magnesium. Other essential components in the mechanism of carbohydrate oxidation include flavo-protein, the dietary precursor of which is riboflavin, coenzymes I and II, the dietary precursor of which is niacin amide, adenosine triphosphate and the iron containing cytochrome system.³⁶ Bollman³⁷ has demonstrated that rats partially depleted of their stores of B vitamins and subsequently maintained with dextrose have a longer survival time if thiamine also is administered. No appreciable further effect was noted when the other B vitamins were supplied. Apparently the period of depletion had affected the body stores of thiamine more than it had the other factors of the B complex. Sydenstricker,²² Jolliffe and Goodhart,³⁸ and

35. Daum, Kate; Boyd, Kathryn, and Paul, W. D.: Influence of Fever Therapy on Blood Levels and Urinary Excretion of Ascorbic Acid, *Proc. Soc. Exper. Biol. & Med.* **40**: 129 (Jan.) 1939.

36. Goodhart, Robert, and Bueding, Ernest: Carbohydrate Metabolism in Practice of Medicine, *M. Clin. North America* **37**: 315 (March) 1943.

37. Bollman, J. L.: Dextrose Administration and Vitamins B, *Proc. Soc. Exper. Biol. & Med.* **50**: 18 (May) 1942.

38. Jolliffe, Norman, and Goodhart, Robert: Beriberi in Alcohol Addicts, *J. A. M. A.* **111**: 380 (July 30) 1938.

Spies³⁹ have reported the precipitation of deficiency diseases in man by dextrose infusions. Sydenstricker²² believes that "waterlogging" after the parenteral administration of dextrose and saline solution is more often a manifestation of deficiency than otherwise. The preventive practice of simultaneously administering thiamine, riboflavin and niacin anide along with each dextrose infusion is based on sound theoretical and practical considerations.

Excessive consumption of carbohydrate acts in the same way as parenteral administration of dextrose and there is much evidence in the literature that this is a common method of inducing deficiency diseases.⁴⁰ Stepp and Schroeder⁴¹ and Germain, Morvan and Babin⁴² have reported instances of beriberi occurring in persons who would have had an adequate thiamine intake except for their unusually high carbohydrate diet. Jolliffe and his co-workers⁴³ have demonstrated the same phenomenon in alcoholic patients.

Interference with Absorption.—As our knowledge of deficiency diseases increases it becomes more and more evident that disturbances of absorption from the intestinal tract play an important role in the production of deficiency disease. As pointed out by Beams, Free and Glenn,⁴⁴ absorption may be impaired because of anatomic, chemical or physiologic changes. These changes are mediated by reduced absorbing surfaces, altered secretions and hypermotility, and further modified by various alkalis, adsorbents and lubricants introduced by the mouth. The more common of these conditioning factors are listed in table 5.

In the diarrheal diseases hypermotility plays the most important role, since the rapid passage of food through

39. Spies, T. D.; Cooper, Clark, and Blankenhorn, M. A.: The Use of Nicotinic Acid in the Treatment of Pellagra, *J. A. M. A.* **110**: 622 (Feb. 26) 1938.

40. Reviewed by Williams, R. R., and Spies, T. D.: *Vitamin B₁ (Thiamine) and Its Use in Medicine*, New York, Macmillan Company, 1938.

41. Stepp, W., and Schroeder, H.: Beriberierkrankung beim Menschen hervorgerufen durch übermassigen Zuckergenuss, München. Med. Wchnschr. **83**: 763 (May 8) 1936.

42. Germain, A.; Morvan, A., and Babin, R.: Alimentary Disequilibrium and Intestinal Fermentation as a Cause of Beriberi, *Bull. Soc. Path. Exot.* **31**: 147, 1938.

43. Jolliffe, Norman; Colbert, C. N., and Joffe, P. M.: Observations on the Etiologic Relationship of Vitamin B (B₁) to Polyneuritis in the Alcohol Addict, *Am. J. M. Sc.* **191**: 515 (April) 1936. Jolliffe, Norman, and Colbert, C. N.: The Etiology of Polyneuritis in the Alcohol Addict, *J. A. M. A.* **107**: 642 (Aug. 29) 1936.

44. Beams, A. J.; Free, A. H., and Glenn, F. M.: The Absorption of Galactose from the Gastrointestinal Tract in Deficiency Diseases, *Am. J. Digest. Dis.* **8**: 415 (Nov.) 1941.

the intestinal tract leaves little time for digestion, solution and absorption of the essential factors. In the more chronic diarrheal states, as in sprue or chronic ulcerative colitis, reduction of absorbing surfaces may be equally important. The clinical importance of diarrhea in producing deficiency disease is evidenced by the many recent reports of pellagra, beriberi, scurvy, riboflavin deficiency, vitamin A deficiency, protein deficiency edema and hypocalcemia induced by this conditioning factor.⁴⁵

Achlorhydria may impair the absorption of ascorbic acid⁴⁶ and of thiamine.⁴⁷ Because of its prevalence particularly in elderly people, achlorhydria always should be suspected in unexplained malnutrition, and malnutrition should be looked for in every subject having achlorhydria.

The role of bile salts in the absorption of the fat soluble vitamins, particularly K, is so well known⁴⁸ that it needs only to be mentioned.

The role of vitamin deficiencies themselves in acting as a conditioning factor by impairing absorption is just

45. Jolliffe, Norman, and Rosenblum, L. A.: The Oral Manifestations of Vitamin Deficiencies, *J. A. M. A.* **117**: 2245 (Dec. 27) 1941. Breese, B. B., Jr., and McCoord, A. B.: Vitamin A Absorption in Celiac Disease, *J. Pediat.* **15**: 183 (Aug) 1939. May, C. D., and McCreary, J. F.: Absorption of Vitamin A in Celiac Disease; Interpretation of Vitamin A Absorption Test, *ibid.* **18**: 200 (Feb.) 1941. Goldberg, H. K., and Schlivek, Kaufman: Necrosis of the Cornea Due to Vitamin A Deficiency; Report of a Case, *Arch. Ophth.* **25**: 122 (Jan.) 1941. Albright, Fuller, and Stewart, J. D.: Hypovitaminosis of All Fat Soluble Vitamins Due to Steatorrhea, *New England J. Med.* **223**: 339 (Aug. 15) 1940. Spies, T. D.; Walker, A. A., and Woods, A. W.: Pellagra in Infancy and Childhood, *J. A. M. A.* **113**: 1481 (Oct. 14) 1939. Bean, W. B., and Spies, T. D.: Vitamin Deficiencies in Diarrheal States, *ibid.* **115**: 1078 (Sept. 28) 1940. Carruthers, L. B.: Pellagra in India, *Tr. Roy. Soc. Trop. Med. & Hyg.* **35**: (July) 1941. Alport, A. C.; Ghalioungui, P., and El Ghariny, Abbas: Defective Gastrointestinal Absorption in Pellagra, *J. Egypt. M. A.* **22**: 191 (April) 1939. Clark, R. L., Jr.: Vitamin Deficiency Complicating Chronic Ulcerative Colitis, *Proc. Staff Meet., Mayo Clin.* **13**: 232 (April 13) 1938. McLester, J. S.: Nutrition and Diet in Health and Disease, ed. 3, Philadelphia and London, W. B. Saunders Company, 1940.

46. Alt, H. L.; Chinn, Herman, and Farmer, C. J.: The Blood Plasma Ascorbic Acid in Patients with Achlorhydria (Pernicious and Iron Deficiency Anemia), *Am. J. M. Sc.* **107**: 229 (Feb.) 1939. Wright, I. S., and Ludden, J. B.: Treatment with Vitamin C (Cevitamic Acid—Ascorbic Acid); Method for Compensating for the Factor of Error Due to Renal Retention of Vitamin C Found in All Previous Saturation and Blood Tests, *M. Clin. North America* **34**: 743 (May) 1940.

47. Melnick, Daniel; Robinson, W. D., and Field, Henry, Jr.: Fate of Thiamine in the Digestive Secretions, *J. Biol. Chem.* **133**: 49 (March) 1941. Field, Henry, Jr.; Robinson, W. D., and Melnick, Daniel: Destruction of Thiamine by Unacidified Bile and Pancreatic Juice: A Possible Explanation of the Cord Changes in Pernicious Anemia, *J. Clin. Investigation* **19**: 791 (Sept.) 1940.

48. Reviewed by Spies, T. D., and Butt, H. R., in Duncan.²⁰ Butt, H. R., and Snell, A. M.: Vitamin K, Philadelphia and London, W. B. Saunders Company, 1941.

beginning to be recognized. The intestinal absorption of galactose and probably other sugars is impaired in experimental B complex deficiencies in the rat⁴⁹ and in the dog.⁵⁰ Groen⁵¹ has shown reduced absorption of dextrose in deficiency states, and Beams, Free and Glenn⁴⁴ have also shown impaired absorption of galactose from the intestinal tract in patients suffering from pellagra, sprue and rosacea keratitis. After therapy, absorption returned to normal in the pellagrins and in some of the patients with rosacea keratitis, but in none of the patients with sprue. Lepore and Golden⁵² have reported x-ray evidence of a characteristic small intestine lesion in some cases of deficiency diseases which could be cured by B complex therapy. They believe that the impaired absorption was caused by disturbances in motility. Recent reports⁵³ indicate that carcinoma of

TABLE 5.—*Factors Interfering with Absorption*

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|--|--|
| <ol style="list-style-type: none"> 1. Gastrointestinal diseases associated with hypermotility or reduction of absorbing surfaces 2. Achlorhydria 3. Biliary disease, especially obstructive jaundice 4. Vitamin deficiency 5. Therapy | <p>Liquid petrolatum, colloidal adsorbents, severe catharsis, gastric or intestinal resections and short circuiting operations</p> |
|--|--|
-

the intestinal tract causes defective absorption of vitamin A which can be corrected by B complex therapy.

Therapy may play an important role in interfering with absorption. Gastrointestinal surgery, particularly resection and short circuiting operations,⁵⁴ has long been known to produce macrocytic anemia similar to addisonian pernicious anemia, and there are many case reports to indict it as a factor in the production of

49. Leonards, J. R.; Free, A. H., and Myers, V. C.: The Effect of Vitamin B Deficiency in the Intestinal Absorption of Galactose in the Rat, Am. Chem. Soc. Spring Meet., Memphis, Tenn., 1942.

50. Free, A. H.; Leonards, J. R., and Myers, V. C.: Studies on the Absorption and Metabolism of Galactose and Glycine in Dogs with Vitamin B Deficiency, meeting of Am. Soc. Biol. Chemists, Boston, April 1942.

51. Groen, Juda: The Absorption of Glucose from the Small Intestine in Deficiency Disease, New England J. Med. **218**: 247 (Feb. 10) 1938.

52. Lepore, M. J., and Golden, Ross: A Syndrome Due to Deficiency of Vitamin B Complex, J. A. M. A. **117**: 918 (Sept. 13) 1941.

53. Abels, J. C.; Gorham, A. T.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract: I. Plasma Vitamin A Levels in Patients with Malignant Neoplastic Disease, Particularly of the Gastrointestinal Tract, J. Clin. Investigation **20**: 749 (Nov.) 1941.

54. McLester, J. S.. Personal communication to the author.

other deficiency syndromes.⁵⁵ Ingestion of liquid petrolatum daily or almost daily is a common practice among many people who are well except for constipation of varying degrees. That such an agent interferes with the absorption of fat soluble vitamins has been indicated by a number of observers.⁵⁶

Interference with Utilization.—This factor is extremely complex and difficult for direct experimental verification. Evidence for interference with utilization is largely circumstantial. In the presence of an adequate intake it is necessary to rule out malabsorption, increased destruction in the bowel, excessive excretion and abnormal requirement before concluding that utilization is defective. It is known for instance that the body must convert carotene to vitamin A, phosphorylate thiamine to cocarboxylase and convert nicotinic acid as its amide to coenzymes I and II, and that riboflavin is essential to more enzyme systems than any other of the known vitamins. Some of these changes may occur in tissue cells in general, but the evidence at this time indicates that the liver is the main organ in which these processes take place. Be that as it may, it is in hepatic disturbances that malutilization is most frequently encountered. In the presence of liver dysfunction these disturbances may be due not only to failure of conversion but to inability of the liver to store²² a nutrient. The body is then dependent on the day to day intake. This intake naturally varies, with the result that an excess today cannot be stored for a deficit almost certain to occur on some future day.

55. Meulengracht, E.: Pernicious Anemia in Intestinal Stricture, *Acta med. Scand.* **72**: 231, 1929. Strauss, M. B.: The Role of the Gastrointestinal Tract in Conditioning Deficiency Disease, *J. A. M. A.* **103**: 1 (July 7) 1934. Richardson, Wyman: Pernicious Anemia Due to Enterocenterostomy: Report of a Case Cured by Reoperation, *New England J. Med.* **218**: 374 (March 3) 1938.

56. Dutcher, R. A.; Harris, P. L.; Hartzler, E. R., and Guerrant, N. B.: Vitamin Studies: XIX. The Assimilation of Carotene and Vitamin A in the Presence of Mineral Oil, *J. Nutrition* **8**: 269 (Sept.) 1934. Curtis, A. C., and Kline, E. M.: Influence of Liquid Petrolatum on the Blood Content of Carotene in Human Beings, *Arch. Int. Med.* **63**: 54 (Jan.) 1939. Andersen, Oluf: Influence of Liquid Petrolatum on the Absorption of Vitamin A in Man, *Acta paediat.* **34**: 422, 1939. Javert, C. T., and Macri, Cesira: Prothrombin Concentration and Mineral Oil, *Am. J. Obst. & Gynec.* **42**: 409 (Sept.) 1941. Elliott, Margaret C.; Isaacs, Bertha, and Ivy, A. C.: Production of "Prothrombin Deficiency" and Response to Vitamins A, D and E, *Proc. Soc. Exper. Biol. & Med.* **43**: 240 (Feb.) 1940. van Eckelen, M., and Pannevis, W.: Absorption of Carotenoids from the Human Intestine, *Nature* **141**: 203 (Jan. 29) 1938. Shelling, D. H.: Calcium and Phosphorus Studies: XIII. The Effect of Emulsification on the Potency of Viosterol in the Treatment of Rickets in Children, *J. Pediat.* **10**: 748 (June) 1937.

The more common illnesses associated with impaired utilization are listed in table 6. A tissue deficiency in vitamin A attributable to impaired conversion of carotene to vitamin A has been reported in liver cirrhosis,⁵⁷ diabetes mellitus,⁵⁸ obstructive jaundice⁵⁹ and hypothyroidism.⁶⁰ The low plasma levels of vitamin A observed at times in patients having gastrointestinal cancer have been explained as a failure to utilize due to hepatic dysfunction.⁵⁸ The high frequency of nutritional diseases in chronic alcohol addicts⁶¹ is well known. Hepatic dysfunction undoubtedly plays a role in these cases. The prevalence of abnormal dark adaptation in hypothyroidism has been thought to imply that the thyroid hormone plays a part in the conversion of the carotene to vitamin A.⁶⁰

TABLE 6.—*Factors Interfering with Utilization*

-
- | | |
|-------------------------------|---|
| 1. Hepatic dysfunction, as in | |
| | Liver disease, diabetes mellitus, alcoholism |
| 2. Hypothyroidism | |
| 3. Malignancy | |
| 4. Therapy | |
| | Sulfonamide drugs, radiation therapy, phenytoin |
-

Therapy also may interfere with the utilization of vitamins. Although deficiency disease produced by sulfonamide compounds has been attributed mainly to

57. Ralli, Elaine P.; Papper, Emanuel; Paley, Karl, and Bauman, Eli: Vitamin A and Carotene Content of Human Liver in Normal and Diseased Subjects: An Analysis of One Hundred and Sixteen Human Livers, *Arch. Int. Med.* **65**: 102 (July) 1941. Ralli, Elaine P.; Bauman, Eli, and Roberts, L. B.: The Plasma Levels of Vitamin A After Ingestion of Standard Doses: Studies in Normal Subjects and Patients with Cirrhosis of the Liver, *J. Clin. Investigation* **20**: 709 (Nov.) 1941. Haig, Charles, and Patek, A. J., Jr.: Vitamin A Deficiency in Laënnec's Cirrhosis: The Relative Significance of the Plasma Vitamin A and Carotenoid Levels and the Dark Adaptation Time, *ibid.* **21**: 309 (May) 1942.

58. Brazer, J. G., and Curtis, A. C.: Vitamin A Deficiency in Diabetes Mellitus, *Arch. Int. Med.* **65**: 90 (Jan.) 1940.

59. Stewart, J. D., and Rourke, G. M.: Vitamin A Metabolism in Obstructive Jaundice, *J. Clin. Investigation* **20**: 453 (July) 1941.

60. Wohl, M. G., and Feldman, J. B.: Vitamin A Deficiency in Disease of the Thyroid Gland: Its Detection by Dark Adaptation, *Endocrinology* **24**: 389 (March) 1939.

61. Jolliffe, Norman: Vitamin Deficiencies and Liver Cirrhosis in Alcoholism: Introduction and Part I, *Quart. J. Stud. on Alcohol* **1**: 517 (Dec.) 1940; Vitamin Deficiencies and Liver Cirrhosis in Alcoholism: Part II. Circulatory Disturbances; Part III: Pellagra, *ibid.* **1**: 727 (March) 1941. Jolliffe, Norman; Wortis, Herman, and Stein, M. H.: Vitamin Deficiencies and Liver Cirrhosis in Alcoholism: Part IV. The Wernicke Syndrome; Part V. Nicotinic Acid Deficiency Encephalopathy, Part VI. Encephalopathies with Possible Nutritional Involvement, *ibid.* **2**: 73 (June) 1941. Jolliffe, Norman, and Jellinek, E. M.: Vitamin Deficiencies and Liver Cirrhosis in Alcoholism: Part VII. Cirrhosis of the Liver, *ibid.* **2**: 544 (Dec.) 1941.

sterilization of the intestinal tract and inhibition of intestinal synthesis of certain factors.⁶² West⁶³ has shown that diarrhea and weight loss in dogs induced by nicotinic acid deficiency and correctable by giving nicotinic acid was not corrected if sulfapyridine was given with the nicotinic acid. On the other hand, raw liver would cure these dogs even in the presence of sulfapyridine, suggesting that sulfapyridine inhibits the action of nicotinic acid but not of the preformed coenzymes present in raw liver. To test out the clinical importance of this finding I have maintained 5 pellagrins in relapse with a basal diet poor in nicotinic acid and administered sulfapyridine in sufficient quantities to obtain a blood level of 8 to 12 mg. One Gm. of sulfapyridine was thereafter administered every four hours, and 400 to 1,000 mg. of nicotinic acid was administered by mouth daily. All the signs and symptoms of pellagra responded as promptly as could be expected if sulfapyridine had not been administered. With the doses of nicotinic acid given (probably excessive) I failed in these few cases to observe any inhibiting effect of sulfapyridine.

Rhoads⁶⁴ has produced cancer in susceptible rats by administering a carcinogen. This action was completely prevented by feeding yeast and partially prevented by riboflavin and casein. With in vitro experiments it then was shown that butter yellow blocked the function of coenzyme I. A constituent of this enzyme is nicotinic acid amide. Rhoads concluded "that the administration of at least one carcinogenic chemical injured normal cells by interfering in some way with an enzyme system which is essential for their normal chemical and so their normal life. The results suggested, furthermore, that this principle of the poisoning by a specific chemical of at least one, and possibly more than one, normal enzyme system caused the normal cell to become a cancer cell. . . ." Furthermore, these studies "suggest the necessity of a complete and precise examination of a large number of patients having malignant

62. Daft, S. S.; Ashburn, W. L., and Sebrell, W. H.: Biotin Deficiency and Other Changes in Rats Given Sulfamylguanidine or Succinyl-sulfathiazole in Purified Diets, *Science* **90**: 321 (Oct. 2) 1942.

63. West, Randolph: Inhibition by Sulfapyridine of the Curative Action of Nicotinic Acid in Dogs, *Proc. Soc. Exper. Biol. & Med.* **40**: 369 (March) 1941.

64. Rhoads, C. P.: Recent Studies in Production of Cancer by Chemical Compounds: The Conditioned Deficiency as a Mechanism, *Bull. New York Acad. Med.* **18**: 53 (Jan.) 1942.

neoplasms in order to ascertain whether or not they show any evidence of an interference with chemical systems of which vitamins form essential compounds." Drake and his co-workers⁶⁵ have shown in guinea pigs that phenytoin produces a rapid and progressive fall in the blood ascorbic acid level and recently he⁶⁶ has shown that phenytoin lowers the blood ascorbic acid level in human beings. Similarly radiation sickness has been attributed to failure of coenzyme formation from thiamine or nicotinic acid or both.⁶⁷

Increased Excretion.—The role of increased excretion of vitamins in the production of malnutrition has received little attention, although the production of hypoproteinemia by albuminuria, and salt depletion either by excessive sweating or by polyuria, are well known phenomena. The possible factors causing increased excretion are listed in table 7. I know of no case report in the literature in which a vitamin deficiency was thought to be produced solely by this conditioning factor. Cowgill⁶⁸ has shown, however, that vitamin B₁ deficiency symptoms appear earlier in dogs maintained with a forced water intake than in dogs that were permitted to drink water ad libitum. He attributed this to increased excretion of vitamin B₁. The possibility of "washing out" the water soluble vitamins must therefore be considered in uncontrolled diabetes mellitus and diabetes insipidus. The loss of vitamins by lactation may be a precipitating factor for deficiency diseases. I have seen 3 patients with severe gestational polyneuropathy who had had only minor symptoms during pregnancy but who rapidly developed severe polyneuropathy during the second week post partum. It was felt that the drain of lactation was the final straw in the pathogenesis of this severe thiamine deficiency.

Methods for determining vitamins in the sweat are technically difficult and not yet satisfactory, so that the

65. Drake, M. E.; Gruber, C. M.; Haury, V. G., and Hart, E. R.: The Effects of Sodium Diphenyl Hydantoinate (Dilantin) on Blood Ascorbic Acid Level in Guinea Pigs, *J. Pharmacol & Exper. Therap.* **72**: 383 (Aug.) 1941.

66. Drake, M. E.: Personal communication to the author.

67. Dietel, I.: Leberextract gegen roentgenkaten, *Strahlentherapie* **48**: 110, 1933. Young, B. R.: Liver Extract as a Remedy for Roentgen Sickness, *Am. J. Roentgenol.* **35**: 681, 1936. Webster, J. H. Douglas: X-Ray Sickness Treated Successfully with Liver Extract, *Brit. M. J.* **1**: 15 (Jan. 6) 1934.

68. Cowgill, G. R.: Vitamin B Requirement of Man, New Haven, Yale University Press, 1934.

practical significance of vitamin depletion by excessive perspiration has yet to be shown convincingly.

By increasing excretion, therapy may contribute to the production of deficiency disease. The forcing of fluids, especially over long periods of time as in certain urinary tract infections, and the loss of fluids by diuresis as in anasarca may be the last straw required to produce a deficiency. Salicylates have been reported⁶⁹ to increase urinary excretion of ascorbic acid, but Youmans and his co-workers⁷⁰ could not confirm this observation.

Increased Destruction.—Increased destruction of vitamins may occur in the gastrointestinal tract prior to

TABLE 7.—*Factors Increasing Excretion*

1. Polyuria, as in
Diabetes mellitus, diabetes insipidus
2. Lactation
3. Excessive perspiration
4. Therapy
Long continued excessive fluid intake, as in urinary tract infections

TABLE 8.—*Factors Increasing Destruction*

1. Achlorhydria	"
2. Lead poisoning ?; trinitrotoluene poisoning ?	
3. Therapy	
Alkalis, sulfonamides, arsenicals	

absorption or in the tissues following absorption. The conditioning factors thought to cause increased destruction of vitamins in human beings are listed in table 8. This list does not include either induced thiamine deficiency in animals caused by enzymatic destruction of thiamine by raw carp or of biotin deficiency in man induced by egg white injury, as neither has been shown to occur spontaneously in man, although neither is beyond possibility.

69. Daniels, Amy L., and Everson, Gladys J.: Influence of Acetylsalicylic Acid (Aspirin) on Urinary Excretion of Ascorbic Acid, *Proc. Soc. Exper. Biol. & Med.* **35**:20 (Oct.) 1936. Ritz, N. D.; Samuels, L. T., and Addiss, Gertrude: Effect of Salicylates and Carvone on the Ascorbic Acid Content of Animal Tissues, *J. Pharmacol. & Exper. Therap.* **70**:362 (Dec.) 1940.

70. Youmans, J. B.; Corlette, M. B.; Frank, Helen, and Corlette, Mildred: Failure of Acetylsalicylic Acid to Affect Excretion of Ascorbic Acid (Vitamin C) in Urine, *Proc. Soc. Exper. Biol. & Med.* **36**:73 (Feb.) 1937.

Green⁷¹ and Coombes⁷² and their associates have shown thiamine deficiency to be the cause of Chastek paralysis in silver foxes. This deficiency was caused by raw carp, which, when mixed with the food, causes rapid destruction of thiamine. Cooking the carp effectively destroys its ability to inactivate thiamine. It is not known whether any other variety of fish has this ability. I have recently examined four ship-wrecked sailors whose diet for forty-eight days consisted chiefly of raw fish and raw turtle. None of these men showed clinical evidence of thiamine deficiency, and their blood thiamine levels were within normal range.

Induced biotin deficiency in man has been produced experimentally by Sydenstricker and others.⁷³ He accomplished it by severe dietary restriction plus the feeding of large amounts of raw egg white. The avid-albumin in egg white presumably "fixes" the biotin in the intestinal tract.

The susceptibility of ascorbic acid and thiamine to destruction in alkaline environment has led to some investigation of the role played by achlorhydria and alkaline therapy. Alt, Chinn and Farmer⁴⁶ have shown a 65 per cent destruction of ascorbic acid in three hours at a p_H of 7.95, representing achlorhydric gastric juice, and obtained results on patients with achlorhydria suggesting decreased assimilation of ascorbic acid. Kendall and Chinn⁷⁴ have obtained from the gastric contents and feces of achlorhydric patients bacteria which destroy ascorbic acid and suggest "that the ascorbic acid fermenting strains may gain the ascendancy in the alimentary canal of certain persons, leading in them

71. Green, R. G.: Chastek Paralysis: A New Disease of Foxes, *Minnesota Wildlife Disease Investigation* 2:106 (Jan.) 1936; Chastek Paralysis, *ibid.* 3:83 (April) 1937; Chastek Paralysis, *Am. Fur Breeder* 11:4 (July) 1938; Chastek Paralysis in Nursing Fox Pups, *ibid.* 11:6 (Sept.) 1938; Seasonal Occurrence of Chastek Paralysis, *ibid.* 11:34 (Feb.) 1939. Green, R. G., and Evans, C. A.: Deficiency Disease of Foxes, *Sc. 22*:154 (Aug. 10) 1940. Green, R. G.; Carlson, W. E., and Evans, C. A.: Deficiency Disease of Foxes Produced by Feeding Fish; B₁ Avitaminosis Analogous to Wernicke's Disease of Man, *J. Nutrition* 21:243 (March) 1941.

72. Coombes, A. I.: Feeding Fish to Fur Bearing Animals, *Am. Natl. Fur and Market J.* 19:5 (Oct.) 1940; Nutrition and Proper Feeding of Foxes and Minks, *ibid.* 20:13 (Aug.-Sept.) 1941. Spitzer, E. H.; Coombes, A. I.; Elvehjem, C. A., and Wisnicky, W.: Inactivation of Vitamin B₁ by Raw Fish, *Proc. Soc. Exper. Biol. & Med.* 48:376 (Oct.) 1941.

73. Sydenstricker, V. P.; Singal, S. A.; Briggs, A. P.; De Vaughn, N. M., and Isbell, Harris: Observations on the "Egg White Injury" in Man and Its Cure with a Biotin Concentrate, *J. A. M. A.* 118:1199 (April 4) 1942; *abstr. Science* 95:176 (Feb. 13) 1942.

74. Kendall, A. I., and Chinn, Herman: The Decomposition of Ascorbic Acid by Certain Bacteria; *Studies in Bacterial Metabolism CIX, J. Infect. Dis.* 62:330 (May-June) 1938.

to a detectable ascorbic acid deficit." Wright and Ludden⁴⁶ have also observed signs of vitamin C deficiency in persons with achlorhydria in spite of a liberal ascorbic acid intake. They were also able to demonstrate lack of absorption in these subjects after an oral test dose.

Melnick, Robinson and Field⁴⁷ have shown that thiamine is stable in gastric juice over a p_H range of 1.5 to 8.0 during sixteen hours of incubation. In the presence of added antiacids the thiamine is completely destroyed, and in the presence of bile or pancreatic juices 50 to 90 per cent was destroyed. The same investigators noted subnormal urinary excretion of a test dose of thiamine in subjects who were given alkalis. Tests in this laboratory by Goodhart⁷⁵ also indicate that achlorhydria may interfere with the absorption of thiamine.

Recent investigations indicate that some of the vitamins, particularly ascorbic acid, may play a prominent role in the detoxications. Martin, Fisher and Thompson⁷⁶ have reported that ascorbic acid, cystine, aminoacetic acid and calcium gluconate definitely reduced the acute toxic manifestations of sulfanilamide, sulfathiazole and sulfapyridine in rats, while thiamine and nicotinic acid were ineffective. Holmes and his associates⁷⁷ have concluded that toxic lead compounds react with ascorbic acid to form a poorly ionized nontoxic salt of lead. The data of Farmer, Abt and Aron⁷⁸ indicate that the lowering of plasma ascorbic acid in neoparsphenamine therapy may be the consequence of an attempt on the part of the body to detoxify the drug. The recent findings of Drake⁷⁹ on phenytoin, previously discussed in the section on malutilization, also may be explained as a diversion of ascorbic acid to detoxify this drug.

CONCLUDING COMMENT

The term malnutrition signifies not a dietary inadequacy but a tissue deficiency of an essential nutrient.

75. Goodhart, Robert: Unpublished observations.

76. Martin, G. J.; Fisher, C. V., and Thompson, M. R.: Therapeutic and Prophylactic Detoxification of Sulfanilamide, Sulfapyridine and Sulfathiazole, *Ann. Int. Med.* **69**: 662 (April) 1942.

77. Holmes, H. N.; Campbell, Kathryn, and Amberg, E. J.: The Effect of Vitamin C on Lead Poisoning, *J. Lab. & Clin. Med.* **24**: 1119 (Aug.) 1939.

78. Farmer, C. J.; Abt, A. F., and Aron, H. C. S.: Influence of Arsenicals, Bismuth and Iron on the Plasma Ascorbic Acid Level, *Proc. Soc. Exper. Biol. & Med.* **44**: 495 (June) 1940.

79. Drake, Gruber, Haury and Hart.²⁶ Drake.⁶⁶

This tissue deficiency may be caused by the failure to ingest an adequate diet. This tissue deficiency may also be caused by factors which interfere with ingestion, absorption or utilization of essential nutrients or by factors that increase the requirement for vitamins, their destruction or excretion. These are known as conditioning factors and when a deficiency disease is produced through their mediation it is known as a conditioned deficiency disease or conditioned malnutrition. The more common illnesses, physiologic factors and therapeutic measures that may produce a conditioned deficiency disease have been listed and briefly discussed. These findings warrant the conclusion that many diseases and some of the therapeutic measures used to combat them interfere with nutrition and are potent factors in the production of deficiency diseases. It is also an inescapable conclusion that the treatment of malnutrition is in each person an individual medical problem requiring exact diagnosis and therapeutic measures which cannot with safety be left in the hands of nonmedical persons. The physician who does so is derelict in his duty to his patient.

CHAPTER XXV

PRINCIPLES OF DIET IN THE TREATMENT OF DISEASE

TOM D. SPIES, M.D.
CINCINNATI

Although the importance of diet in the treatment of disease was emphasized by Greek and Roman physicians, a true conception of the value of food as a therapeutic agent has been gained only in recent years. The many ramifications of our knowledge concerning food could not be listed, let alone described adequately, within the scope of this paper. The administration of indicated foodstuffs or their specific constituents to persons with specific deficiency diseases is followed by miraculous improvement. The judicious use of these specific substances as therapeutic agents is revolutionizing the practice of medicine. Even more benefits to mankind would follow the application of this knowledge toward the prevention of these nutritional diseases. Certain it is that proper nutrition is essential for the health and vigor of the higher forms of life, and every living cell in the human body requires specific nutrients. Though the cell must have these nutrients, some of them it cannot always make. Accordingly, they must be supplied if the body is to function normally.

Respiration and growth of cells involve the synthesis of complex substances from simple ones. When the available simple compounds are inadequate to supply the needs of the body, as the result of inadequate assimilation, increased demand, increased loss or a decreased supply, a disorder is initiated and factors which operate to maintain nutritional balance are brought into play. These beneficial mechanisms may act very efficiently at first and against lesser odds when the detrimental factors are not too protracted. Excessive physical exercise, acute infections and fever affect adversely those factors which tend to maintain nutritional balance. In the beginning of many deficiency diseases, levels of the essential substances in some tissues are decreased at the expense of others. In other

words, there is a protective homeostatic control of the storage and distribution of many of these substances vital to the cells. Equilibration becomes more and more difficult to achieve as time goes on. One could say, perhaps arbitrarily, that the dietary deficiency development is under way and that at least a biochemical lesion is present. When this lesion is severe enough, functional disturbances arising from various parts of the body become manifest. Vasomotor instability in the skin, functional disorders of the alimentary tract, nervous system or circulatory system may occur. There is no regular order to the appearance of these symptoms, and presumably they are affected by hereditary predisposition or trauma in the wear and tear of everyday life. Certain it is that the clinical picture is complex and is composed of an infinite variety of symptoms. After many months of severe or persistent symptoms, accompanied perhaps by slight chemical and physiologic alterations, structural changes begin to appear in the various tissues, and ultimately the clinical diagnosis can be made.

The practicing physician who at last is called on to treat a case of clinical deficiency disease is faced with a nutritive breakdown. Yet he has little information of the previous nutritional status of the patient, a factor of great importance in restoring and maintaining his health. Since 1936 my associates and I have been faced with the same problem and, like the practicing physician, we realized the necessity of initiating immediate therapy. At the same time, however, we have been especially interested in devising methods of persistent therapy of a type which would eliminate such dicta as "once a pellagrin, always a pellagrin." Accordingly, in treating each patient we began the long and arduous task of determining the factors responsible for his nutritive breakdown, for it is only by their elimination that one can avoid recurrences. This paper is concerned with the principles of practical therapy which have been derived from the application of the methods outlined to thousands of our cases during the past several years. While other investigators have made similar studies, we are somewhat more familiar with what we have done. Accordingly, we are reporting our methods in some detail with the assurance that they would have the general support of other investigators in the field.

The essence of successful treatment is early and accurate diagnosis. The diagnosis of clinical conditions and the assessment of the nutritional status of a patient and his family can best be made by a conservative interpretation of the data from a dietary and food survey, a complete medical history and physical examination, and special laboratory determinations. The brief outlines which follow serve in our hands to gather partial information of the type needed. As in any other field of medicine, we attempt to gather information about the person as well as his disease; accordingly, it is impossible to give an outline which would suffice in all details for every person.

DIETARY ASSESSMENT

It is of primary importance to obtain a nutrition history when the patient is first seen. If the diet is found inadequate, tentative nutritional deficiencies are suspected, even though there is no diagnostic clinical manifestation at the time. In such instances, repeated dietary evaluation, laboratory studies and general clinical check-ups are made. If the diet seems adequate to meet normal nutritional requirements and the patient has lesions of nutritional failure, we begin our search for some condition which is increasing the nutritive requirements or interfering with the absorption or utilization of nutrients. For several years we have used the type of nutrition history shown in table 1 and have found it satisfactory for the initial studies of a person suspected of nutritional imbalance. Since we have placed ourselves in the position of the practicing physician, we believe this type of history will be a valuable aid to him in collecting data for a precise diagnosis and treatment. This can best be illustrated by the case shown in table 2. By comparing the food eaten by the patient whose nutrition history is shown here with the food she needs, it is apparent that her diet falls far short of being satisfactory. Although this type of nutrition study does not allow an accurate calculation of the various nutrients in the dietary, it has the advantage of not requiring a great deal of time or special training on the part of the persons taking or evaluating the data.

We have found it desirable to make a thorough inventory of the income and food resources of the patient and his family, though it is time consuming, for

TABLE 1.—Nutrition History

Name: Mrs. J. S.	Age: 29	Address: Trussville, Ala.	Date: Oct. 21, 1941
Food—Amount used			
Whole milk—1 cup daily		Breads	
Skimmed milk—0		Cornbread—3 or 4 large pieces daily	
Canned milk—0		Biscuit—5 or 6 daily	
Cheese—0		Loaf bread: white—0; whole wheat—0	
Butter—0		Crackers—0	
Other fats—pork fat—liberal amount		Cereals	
Eggs—3 weekly		Rice—0	
		Grits—1 serving daily	
Meats		Oatmeal—0	
Lean meat (beef, lamb, pork)—0		Others—0	
Liver—0		Desserts—0	
Fat meat—0		Sugar—4 or 5 teaspoons daily	
Fish—1 medium size serving about once a month		Syrup—2 tablespoons daily	
Poultry—0		Other foods—0	
Salt pork—1 serving daily (about 1 ounce)		Yeast	
Vegetables and Fruits		Other vitamins—0	
Potatoes, Irish—3 large servings weekly		Beverages	
Potatoes, sweet—0		Tea—0	
Dried vegetables—1 serving daily		Coffee—2 cups daily	
Greens—3 servings weekly		Soft drinks	
Tomatoes—0		Alcoholic beverages—0	
Other vegetables		Snuff—yes	
Cooked—seldom used		Other tobacco—0	
Raw—seldom used		Appetite—poor—some days eats less bread	
Orange—0		How long was this diet used?—past year	
Grapefruit—0			
Dried fruit—0			
Other fruit—0			

not infrequently this material gives us a lead in determining the adequacy of his diet. If the income is low and food resources are meager, it is almost certain that the diet has been inadequate and it is desirable to study the nutritional status of the patient very carefully. We wish to point out, however, that it is fallacious to consider that an adequate or even a liberal income means

TABLE 2.—*Case Illustrating Unsatisfactory Diet*

Food	Amount Recommended for an Adequate Diet *	Amount Used by Patient
Milk.. . . .	2 cups daily	† 1 cup daily
Eggs.....	3-4 weekly	† 2 weekly
Meats:		
Lean beef, liver, lamb, veal, lean ham or pork, chicken or fish	5-6 small servings weekly	† 1 medium size serving of fish once a month
Salt pork.....	1 serving daily (about 1 ounce)
Vegetables and Fruits:		
Tomato, orange or grapefruit	5 servings weekly	† None
Potato or sweet potato	1-2 servings daily	† 3 servings weekly
Dried vegetables or nuts	4 servings weekly	1 serving daily
Leafy green and yellow vegetables	6 servings weekly	† 3 servings weekly
Other vegetables and fruits	6 servings weekly	† Seldom used
Bread: enriched or whole grain	At every meal	† Liberal amount, but none of it enriched or whole grain
Cereal—whole grain .	At least 1 serving daily	† 1 serving daily but not whole grain
Desserts.....	1 serving daily	† None
Sugar and syrup.....	As desired	Moderate amount
Butter or fortified oleo-margarine	2 tablespoons daily	Liberal amount of pork fat

* Based on "Planning Diets by the New Yardstick of Good Nutrition," Bureau of Home Economics, United States Department of Agriculture, Washington, July 1941.

† Indicates foods of which patient did not eat sufficient amounts.

that the diet has been adequate. Many persons who have liberal funds available for food fail to eat a proper diet. Others whose income is on first glance seemingly too low to provide a good diet, by careful budgeting and a wise selection of food, manage to get what they need to meet their nutritive requirements. But there is a point below which the income and food resources cannot fall and still provide an adequate diet. For example, we found that the minimum cost of the food needed to satisfy National Research Council standards

for a family of five, living in this geographic location, to be \$8.60 a week, whereas a particular family we had studied had a food allowance of \$2.50. No other sources of food, such as a garden, chickens or livestock, were available to them.

Frequently, trained observers keep an accurate record of the patient's food intake for a period of a week or more at various seasons of the year. From this the nutritive value of the dietary is evaluated and the degree of deficiency of his diet is correlated with clinical findings and laboratory tests. Although such a study gives interesting results and has been of some value to us in determining the degree of deficiency of the various nutrients in the dietaries of many of our patients, it is too arduous and time consuming to be used as a routine procedure by the practicing physician. It requires the expenditure of a great deal of time both with the patient and in the calculation of the results. Such a method is practical only if the patient is sufficiently intelligent and cooperative to keep an accurate record of his food intake and if the time and services of a trained nutritionist are available to supervise the collection and summarization of the data and to calculate the nutritive value of the dietaries.

No human being is able to give a dietary history as comprehensive as the physician might wish, and if one was to rely solely on dietary assessment he would fall far short of the goal of accurate diagnosis which is the first requirement for satisfactory therapy.

SYMPTOMS AND PHYSICAL SIGNS

Of necessity the physician must place the greatest reliance on a complete history and physical examination (figs. 1 and 2), as a diagnosis cannot be made except by clinical methods. It is customary in our studies to regard each person individually and to vary somewhat the general history, physical examination and special examinations, depending on the nature of the symptoms he presents. In all instances, information which satisfies the complete history and examination forms as listed in figure 3 is obtained. In addition, special organ systems are studied as indicated. Detailed examination of the mouth is particularly stressed.

When we have satisfied ourselves that the infants and children under our observation receive considerably less than the recommended allowance of essential nutri-

ents, we are willing to accept the following symptoms as suggestive though not diagnostic of deficiency states: loss of desire for food and failure to gain weight; poor muscle tone, and aversion to play; abnormal tardiness

NAME _____		Clinic _____	Hospital _____	Examiner _____	Date _____
Sex _____	Color _____	Age _____	Weight _____		
Family History of Pellagra (X had disease, D died of disease; - negative)					
Mother _____	Brother _____	Uncle _____	Husband _____		
Father _____	Sister _____	Aunt _____	Wife _____	Children _____	
Past History:		First attack _____	No attacks _____		
Predisposing _____		Precipitating _____	Age of children _____	Length of Lactation _____	
Operations _____			1 _____		
Infections _____			2 _____		
No pregnancies _____			3 _____		
Menstrual _____			4 _____		
			5 _____		
			6 _____		
			7 _____		
			8 _____		
			9 _____		
			10 _____		
Present Illness:		Chief complaint _____	Date of onset _____		
Headache _____		Tinnitus _____			
Dizziness _____		Miscellaneous _____			
Eyes: Burning _____		Blurred vision _____			
Discharge _____		Lacrimation _____			
Night blindness _____		Photophobia _____			
Ears: Hearing _____					
Nose: _____					
Mouth: Teeth: Upper-in _____	Lower-in _____	Tongue-sore _____	Onset _____	Lips-sore _____	onset _____
	out _____	red _____		red _____	
	Sore throat _____	Salivation _____			
Skin: Dermatitis _____	Location _____		Onset _____		
Mental Symptoms: _____		Onset _____			
Hallucinations _____					
Insomnia _____					
Nervousness _____					
G.I. Anorexia _____		Neurological: Pain in legs _____			
Constipation _____		arms _____			
Vomiting _____		Parasthesia _____			
Diarrhea _____		weakness of - _____			
Pain in stomach _____					
Proctitis _____		General: Weakness _____			
		Easy fatigability - _____			
G.U. Vaginitis _____		Skin - burning _____			
Urethritis _____		itching _____			
Perineal lesions _____		Weight loss - _____			
Physical Examination:					
Developed - well _____		Nourished - well _____			
moderately _____		moderately _____			
poorly _____		poorly _____			
Eyes: Pupils _____	React to L. & A. _____				
Conjunctiva _____					
Sclera _____	Circumcorneal injection _____	Inflamed _____			
Cornae _____		Pterygium _____			
Ophthalmoscopic _____	Arcus _____	Mystagmus _____			
Slit lamp _____					
Hair color: _____					
Nose: Sharkskin _____	Nares _____	Nasomalar _____	Nasolabial _____		

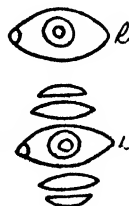


Fig. 1.—Form for recording history.

in sitting, standing and walking, and pain on sitting or standing; insomnia, poor record in school; repeated respiratory infections; chronic diarrhea; photophobia, lacrimation, abnormal dryness and burning of the eyes; pallor; rough skin; fissures and maceration at the

angles of the mouth; abnormally red tongue; increased pulse rate; beading of the ribs; enlarged wrists; square head; serious dental abnormalities, and Vincent's infection.

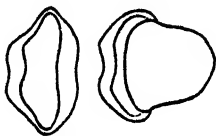
Likewise, in adolescents and adults, the following symptoms occurring in persons known to have ingested inadequate amounts of required nutrients suggest deficiency states: weakness; lassitude; lack of desire for food; loss of weight; failure of mental application; sore mouth or tongue; constipation or diarrhea; nervousness and irritability; paresthesia; night blindness; photophobia; burning and itching of the eyes; lacrimation; general pains in the muscles or joints; Vincent's infection; cheilosis; red, swollen lingual papillae; glossitis, stomatitis, vaginitis, poor muscle tone, loss of vibratory sensation; alteration of tendon reflexes; hyperesthesia of the skin; bleeding gums; dermatitis; abnormal pigmentation of the skin, particularly over the points of pressure; rachitic chest deformity; anemia; abnormal dryness or conjunctival injection of the eyes; vascularization of the cornea; inability to accommodate properly.

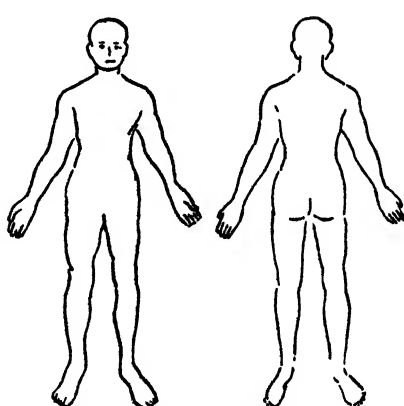
It has been customary to present through textbooks and lectures the manifestations of severe degrees of deficiency diseases. Hence it is little wonder that the milder forms have gone unrecognized and the real incidence is not always fully appreciated. Yet it is highly desirable that the physician make an early and accurate diagnosis in order to initiate therapy which will restore the patient's health before serious structural damage occurs in the tissues. For the most part the arrangement of the descriptive material in the previous chapters has been grouped around one nutrient or one disease arising from a deficiency of a single nutrient. This description certainly is justifiable, but it assumes a degree of simplicity which does not occur in the physician's day to day practice of medicine.

SPECIAL LABORATORY TESTS OF USE IN DIAGNOSIS

After we have analyzed the dietary record, medical history and physical examination and find symptoms in persons whom we suspect of having nutritional deficiency disease, we attempt to gain special information

by means of laboratory tests. While they are not all practical for practicing physicians, facilities for some might be available to some physicians.

Teeth: Caries	Pyorrhea		
Mucous membranes - buccal	Lips (mottling (transverse (atrophy	Angles - Cheilosis crusts fissures scars atrophy pallor redness maceration	
Tongue: Edema atrophy T.M. coated ulcers fissures papillae	Palate - soft hard		
	slit lamp atrophic hypertrophic cobblestone degree Red center - number		
Skin - mottling	sweating	purpura	Triple response Spiders
Face	Knees	Shoulders	
Neck	Shins	Elbows	
Chest	Feet	Forearms	
Back	Toes	Hands	
Abdomen	Perineum	Fingers	Nails
Chest:	Heart	Lungs	B.P.
Abdomen:			
Miscellaneous:			
Neurological:	R	L	
Pain on soles			
Pain on calf			
Knee jerk			
Ankle jerk			
Babinski			
Parasthesia: arm			
leg			
Vibration: arm			
leg			
Dynamometer			
Remarks:			
Deficiency:			
Nicotinic acid			
Thiamin			
Riboflavin			
Vitamin B ₆			
Iron			
Vitamin A			
Vitamin C			
+ mild			
++ moderate			
+++ severe			



Front
Back

Fig. 2. - Continuation of form for recording history.

1. Hemoglobin determinations, red blood cell counts, and packed cell volumes are very important routine measures.

2. X-ray examination of the long bones should be made to detect active and healing rickets, and serum phosphatase and phosphorus determinations to detect early rickets. Serum calcium determinations are also useful.

3. Protein serum albumin determinations by the Kjeldahl technic are especially useful when protein deficiency is suspected.

4. Ascorbic acid determinations on plasma are useful in determining vitamin C subnutrition. Determination of the level in white cells often is made when vitamin C deficiency is advanced.

5. Slit lamp and biomicroscopic examinations of the capillaries in the conjunctiva and cornea are extremely valuable aids.

6. The detection of prothrombin deficiency is applied when vitamin K deficiency is suspected in persons with liver disease, particularly jaundice, or in expectant mothers.

7. The B. E. S. test, the recent colorimetric method described by Beckh, Ellinger and Spies, is of considerable clinical use in detecting small quantities of abnormal pigments in the urine of persons with "sub-clinical" and clinical deficiency states.

8. We frequently do determinations for vitamin A, thiamine, nicotinic acid, riboflavin, pantothenic acid, biotin and pyridoxine. In some instances these laboratory findings can be correlated with the clinical findings; in others, they cannot.

9. Myriads of Vincent's organisms, staphylococci and streptococci can be identified in smears taken from mucous membrane lesions in the mouth or in the vagina. The staphylococci and streptococci often can be isolated in pure culture from the lesions of riboflavin deficiency. The organisms in these lesions disappear rapidly after specific therapy is given to the patient.

10. Gastric analyses are made before and after histamine injections—we determine free hydrochloric acid, pepsinogen and rennin, and in special cases determine the presence or absence of the intrinsic factor of Castle.

SPECIFIC PRINCIPLES OF THERAPY AND SUGGESTED METHODS OF APPLICATION

The more we have studied diseases arising from nutritional imbalance, the more we have become impressed

with the great factor of safety operating to protect the body. Life continues long after deficiency states set in, and there is always a margin of safety between the beginning of ill health and death from nutritional failure. When functions of the tissues become diminished or altered as the result of a deficiency over long periods

															Name _____ No. _____ Address _____ Sex _____ Color _____ Age _____ Birth _____								
No. in Family _____ No. having Pellagra _____ Operations _____ Accidents _____ No. Pregnancies _____ No. Aborts _____																							
ORAL MUCOUS MEMBRANES — DEGREE OF REDNESS																							
S & L M & M	Cheek _____	Inside Lip _____	Ulcers _____	S & V Dil	Palate Hard _____	Soft _____	Floor _____	Ging _____	Ventrals Macro _____	Micro _____													
PERIODONTAL																							
Ging. rite _____		Morph. ty _____		Pockets _____		Calculus _____		Pus _____		Prophy _____		Stagnation _____		Oral Changes _____									
DENTAL																							
Deciduous _____		Curves Permanent _____		Total _____		Missing Teeth _____		Season Lost _____		Eruption _____		Arch Form _____		Occlusion _____		Care _____		Restoration _____					
MEDICAL																							
Taste _____		Smell _____		Anger Dur _____		Int _____		Fear _____		Tongue Teeth Mark _____		Tip _____		Sides _____		Papilla _____		Dermis _____		Metabolic Disturbances _____			
MENTAL PAIN MOOD																							
Legs _____		Concomitant P _____		Spinal Bum _____		Night Hand _____		Nervous _____		Nerveless Miles _____		Arm _____		Leg _____		Head _____		Stom _____		Teeth _____		Stomach _____	
Weight Loss _____		Ties Easy _____		Hair _____		Constipation _____		Starvation _____		X-ray Want _____		Internal _____		Pictures _____		_____		_____		_____			
TREATMENT																							
Skin Dor _____		Burn _____		Response Without Medication _____		Correlation of Oral and Systemic Health _____		Medication _____		Change With Medication _____		Appetite _____		_____		_____		_____					
DIETARY DEFICIENCY																							
Hic. Acid _____		B _____		Riboflavin _____		B ₆ _____		P ₆ _____		A _____		C _____		D _____		Pant _____		Fat _____		Cals _____			
Meat _____		Fat _____		Lean _____		Liver _____		Fruits and Vegetables _____		Milk _____		Vitamin _____		Yeast _____		Eggs _____		_____		_____			
Bread and Cereals _____		Alcohol _____		Tobacco _____		Cigarettes _____		Beans _____		Pipe _____		Cigar _____		Ordinary _____		Breakfast _____		Lunch _____		Dinner _____			

Fig. 3 History and examination form.

of time, there is usually quick restoration of function following adequate amounts of specific therapy. Nevertheless there is a limit to the self regulation, and indeed, at times, to the repair which is possible as a result of therapy. These vital substances frequently must come to the human body from an external source, and, since the body does not conserve all, it is important that a person with nutritional deficiency diseases have as little

activity as possible while repairs to the affected tissue are under way. The specific agents, whether they are food, yeast, liver or extracts of these substances or synthetic vitamins, serve in a natural manner to perform a natural function. The recommendations which are to be made have arisen chiefly from the gratifying experience of having treated over 5,000 consecutive patients with dietary deficiency diseases without a death.

Deficiency diseases are not rare. The apparent mystery surrounding them is due in great part to gaps in our present day knowledge. Nevertheless, the practicing physician should and must apply the best knowledge available to the diagnosis and treatment of nutritional deficiencies. To do so, our experience would lead us to suggest that his diagnosis will depend chiefly on a reliable interpretation of a carefully taken history and a thorough physical examination. When taking the history, the physician should have in mind that deficiencies of the essential nutrients are particularly prevalent in the following four groups:

1. Those who are indigent and have erroneous dietary habits or dietary idiosyncrasies. Many such persons live for a long period of time on a diet low in protein and calories, minerals and vitamins, and relatively high in carbohydrates and fats. These dietaries often contain far too little milk products, lean meat, fish, green vegetables and fruits.

2. Persons with organic disease. The incidence of deficiency diseases is especially high among persons with chronic tuberculosis, diseases of the alimentary tract and cardiovascular system and diabetes, which interfere with the ingestion, assimilation or utilization of the protective substances present in food. Many of these persons have an opportunity to eat sufficient amounts but because of their disease either have lost their desire to eat or are unable to utilize it properly.

3. Too frequently the overzealous physician in treating a certain type of organic disease prescribes a diet so deficient that nutritive failure is gradually induced. While we do not wish to give the impression that all therapeutic diets are necessarily inadequate diets, we not infrequently find patients develop nutritional diseases as the result of restriction to diets prescribed for therapeutic purposes. Figure 4 illustrates some of the deficiencies occurring in diets consumed by persons

RECOMMENDED AMOUNT	PROTEIN GRAMS	CALORIES	CALCIUM GRAMS	IRON MILLIGRAMS	VITAMIN A INTERNATIONAL UNITS	THIAMINE MILLIGRAMS	ASCORBIC ACID MILLIGRAMS	RIBOFLAVIN MILLIGRAMS	NICOTINIC ACID MILLIGRAMS
70	3000	.80	12.0	6000	1.8	75	2.7	18	
ALLERGY DIET	36	2200		9.4	1724	.463	20	.42	10
DIABETIC DIET	60	1730	.41	13.2	5005	.425	166	.734	14
KETOGENIC DIET	50	2530	.35	10.6	5040	.628	57	.482	16
LOW CALORIE DIET	50	1000	31	10.5	2575	.929	221	.780	14
LOW PROTEIN DIET	40	2330	35	8.3	3071	.647	64	MC	5
SUPPLY DIET	60	1720	1.00	7.4	6076	.722	13	.153	13

Fig. 4.—Amounts of nutrients supplied by certain therapeutic diets compared with amounts recommended for an adequate diet.

with nutritional diseases who came to us for treatment. We suggest that the physician prescribing special therapeutic diets check the food recommended with that which he knows is required for the adequate diet. If the restrictions are of such nature that the foods permitted cannot provide the essential nutrients in adequate amounts, it is recommended that he supplement those nutrients as required by use of synthetics or concentrates.

4. Persons with chronic alcoholic addiction. Persons who substitute the calories in alcohol for the calories in food are prone to develop deficiency diseases. If, however, a liberal adequate diet is eaten, deficiency diseases are not likely to occur even when large amounts of alcohol are ingested.

It should be kept in mind that in all groups many undernourished people never develop a clinical sign diagnostic of a specific deficiency disease. Irrespective of whether the deficiency develops following poverty, dietary idiosyncrasies, organic diseases, alcoholic addiction, erroneous dietary habits or any combination, the lesions, symptoms, seasonal incidence and methods of treatment are essentially the same.

Foods, dried brewers' yeast, liver concentrates and synthetic vitamins, and certain minerals, are as much a part of the present day physician's armamentarium as arsphenamine and insulin. To consider diet properly the physician should think in terms of enough dextrose, amino acids, fatty acids, minerals and vitamins. The foods in the alimentary tract are altered through successive steps of digestion and absorbed into the blood stream and passed into the tissues. The proteins are absorbed as amino acids, the carbohydrates as sugars, and the fats as fatty acids. The vitamins and minerals are altered little if any. The body can synthesize only about one half of the different amino acids which are required, and the other half must be provided. Amino acids may be turned into urea or their carbon fractions used to form dextrose, or they may "sacrifice themselves" to protect us from poisonous products. Perhaps they can serve as source material to act with or aid in synthesizing certain compounds of physiologic function still to be identified. Some of these amino acids enter into the

proteins of the tissue and, like the dextrose, the fatty acids, the minerals and the vitamins, become for a time parts of our living tissues.

Long ago we learned that the diagnosis of one clinical syndrome denoting nutritional failure necessitates a thorough search for others. While individual vitamins have special functions, they are wisely administered together. Vitamins A and D, which are members of the fat soluble group, occur together in fish liver oils and are customarily used together therapeutically. Vitamin K is usually classified as a fat soluble compound, though water soluble synthetic compounds having vitamin K activity are available. Vitamin K should be considered as a special substance essential for the maintenance of normal concentration of prothrombin in the blood. Except for the hemorrhagic disease of the newborn, a deficiency is usually the result of faulty absorption rather than inadequacy of vitamin K in the diet. Vitamin E is being extensively studied, but as yet its value in the treatment of diseases of human beings is a matter of conjecture. The vitamins of the B complex are water soluble and found especially in such natural products as yeast and liver. Viable yeast and liver cells function as an active laboratory in producing these substances. They appear to be intimately concerned with carbohydrate metabolism. Ascorbic acid is a member of the water soluble group and is specifically concerned in the prevention and treatment of scurvy.

Too often polyvitamin products have not been as useful as they might have been. It seems wise that the amount of vitamins in mixtures should bear a relationship to the normal daily requirements. The physician in turn may then prescribe amounts of these vitamins as multiples of the estimated daily requirement. Recently, the National Research Council has seen fit to make the recommendations presented in chapter 17.

Where synthetic vitamins, such as riboflavin, nicotinic acid or thiamine, are added to dried brewers' yeast or liver, it is desirable that a substantial amount of the vitamins come from the yeast or liver.

METHODS OF THERAPY

Therapy should be directed along four lines: 1. Conditions causing excessive requirements for nutritional essentials should be removed or relieved wherever

possible. 2. Substances should be administered in sufficient amounts to correct the deficiency. 3. Symptomatic treatment and treatment for coexisting diseases should be given. 4. A liberal amount of a well balanced diet, which has been discussed in other portions of this book, should be prescribed. It is often necessary to combine specific therapy, symptomatic therapy and the treatment of coexisting diseases in order to treat the patient successfully. The very essence of treatment for nutritional diseases lies in the administration of foods rich in proteins, minerals and vitamins, supplemented by specific therapeutic agents. The foods prescribed will depend on the nature of the deficiency and the age, race, habits, tastes and financial status of the patient concerned. The diet should be supplemented with appropriate preparations in terms of dried brewers' yeast or liver extract, or concentrates thereof, or of synthetics or minerals. More specifically, we find that, where clinical syndromes arise from a deficiency of vitamins, a deficiency of many other essential nutrients is likely to exist. It is of prime importance in prescribing for every case to insure the ingestion and retention of a diet which meets the patient's nutritive requirements. This diet must be one that the patient can eat, digest and assimilate. It must be remembered, however, that to rely on dietary therapy is inadvisable and unpractical. Deprivations of the nutrients usually have existed for years and often the deficiency is advanced so that the food the average person can eat is not sufficient to supply the amount of the food factors necessary to restore his health promptly.

Our clinical experience and controlled studies have led us to adopt a policy of mixed vitamin therapy in treating nutritional deficiencies. The amounts of therapeutic substances prescribed necessarily vary considerably from patient to patient and even in the same patient it varies at different times. It is better to prescribe too much than too little, too soon rather than too late. Although there are many ways of treating nutritional deficiencies, we have found that the following therapy gives satisfactory results:

In treating the clinical syndromes of beriberi, pellagra, riboflavin deficiency and scurvy, we use a formula containing 10 mg. thiamine, 50 mg. niacin, 5 mg. riboflavin and 75 mg. ascorbic acid. If the symptoms of one

deficiency predominate we add to the basic formula more of the vitamin specific for the predominating deficiency. In the case of beriberi, 10 mg. of thiamine is added daily; in riboflavin deficiency 5 mg. of riboflavin b. i. d. daily; in scurvy 100 mg. of ascorbic acid t. i. d., and in mild pellagra 50 mg. of niacin amide t. i. d. If the pellagra is severe, the patient is given 150 mg. of niacin amide t. i. d. in addition to the basic formula. When the patient is moribund from nutritive failure due to deficiencies of the vitamin B complex it may be necessary to resort to parenteral injections in order to prolong and indeed even to save life. When large amounts of d-glucose are injected daily, we recommend the inclusion of 20 mg. of niacin amide, 7.5 mg. of riboflavin and 5 mg. of thiamine. In a few instances we have found it desirable to inject 50 mg. of ascorbic acid in isotonic solution of sodium chloride.

Dried brewers' yeast powder, liver extract, wheat germ and rice polishings are excellent therapeutic agents for the treatment of diseases arising from a deficiency of the B complex vitamins. These substances are particularly valuable in that they contain significant amounts of protein and other essential nutrients, and probably vitamins of the B complex as yet unknown. The amount administered depends on the severity of the disease. We usually give daily from 4 to 6 ounces of dried brewers' yeast powder or oral liver extract; from three to four doses of 20 cc. of parenteral liver extract, or from 150 to 300 Gm. of wheat germ. Although other investigators have had success with rice polishings, our experience with it is not wide enough for us to make specific recommendations in regard to its use. Some patients complain of the taste of these materials, in which case we disguise the taste by stirring them into milk or tomato juice or by mixing them with water and adding tomato catsup. They can be added to bouillon, sprinkled over cereals or added to eggnog. We have found that a mixture of approximately 20 per cent dried brewers' yeast by weight added to 80 per cent peanut butter is acceptable to persons who like peanut butter. A mixture of this yeast and peanut butter is practical and if used wisely would go a long way toward correcting the deficiencies of protein, fats, calories and B complex vitamins in the diets of many persons.

In vitamin A deficiency, we give adults 50,000 units of vitamin A daily for at least two months. It may be given in the form of carotene or fish liver oils. The clinical response in vitamin A deficiency is often slow and it may be necessary to continue treatment over a long period of time before beneficial effects are observed.

Children with active mild rickets are given 1,600 I. U. of vitamin D daily in the form of fish liver oils or irradiated ergosterol. To those with advanced rickets, 5,000 I. U. is given, while in rare cases of refractory rickets 50,000 I. U. or more is often administered. We wish to point out that although a daily dose of 800 I. U. is considered the safe prophylactic dose for full term infants, premature infants may require 3,000 I. U. In juvenile, adult and senile rickets large doses of the vitamin D concentrates, 10,000 I. U. daily, should be given for therapeutic purposes.

In hemorrhagic disease due to vitamin K deficiency in the newborn infant we give 1 mg. of vitamin K often by intravenous injection. To adults with vitamin K deficiency we give 1 to 5 mg. usually by the parenteral route. In cases in which bile is excluded from the intestine, orally administered vitamin K, since it is fat soluble, must be accompanied by some bile salt preparation to aid in its absorption.

We never regard the treatment as satisfactory until the patient has gained significantly in strength and his weight has returned to normal. Unfortunately, many physicians take the point of view that deficiency diseases can be overcome by a few days treatment. This is not surprising since the immediate result of therapy is often dramatic. Nevertheless, deficiency diseases which have taken months or even years to develop cannot be eliminated quickly. We have found it wise to keep our adult patients under observation until they return to work and are able to continue to work for several months.

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